

Atlas of Rheumatoid Arthritis

Editor

Paul Emery



Springer Healthcare

Atlas of Rheumatoid Arthritis

Atlas of Rheumatoid Arthritis

Professor Paul Emery, Editor

Published by Springer Healthcare Ltd, 236 Gray's Inn Road, London, WC1X 8HB, UK.

www.springerhealthcare.com

© 2015 Springer Healthcare, a part of Springer Science+Business Media.

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means electronic, mechanical, photocopying, recording or otherwise without the prior written permission of the copyright holder.

British Library Cataloguing-in-Publication Data.

A catalogue record for this book is available from the British Library.

ISBN 978-1-907673-90-0 ISBN 978-1-907673-91-7 (eBook)

DOI 10.1007/978-1-907673-91-7

Although every effort has been made to ensure that drug doses and other information are presented accurately in this publication, the ultimate responsibility rests with the prescribing physician. Neither the publisher nor the authors can be held responsible for errors or for any consequences arising from the use of the information contained herein. Any product mentioned in this publication should be used in accordance with the prescribing information prepared by the manufacturers. No claims or endorsements are made for any drug or compound at present under clinical investigation.

Project editor: Katrina Dorn

Contents

Contributors list	ix
-------------------	----

Editor biography: Professor Paul Emery	xi
--	----

PART ONE RHEUMATOID ARTHRITIS OVERVIEW

1 Classification of rheumatoid arthritis	1
---	----------

References	19
------------	----

2 Pre-rheumatoid arthritis	21
-----------------------------------	-----------

What is pre-rheumatoid arthritis?	21
-----------------------------------	----

Risk factors for rheumatoid arthritis	21
---------------------------------------	----

Systemic autoimmunity associated with rheumatoid arthritis	22
--	----

Symptoms without clinical arthritis	23
-------------------------------------	----

Unclassified arthritis	23
------------------------	----

References	32
------------	----

3 Early rheumatoid arthritis	35
-------------------------------------	-----------

Introduction	35
--------------	----

Pathology in early rheumatoid arthritis	37
---	----

Diagnosis of early rheumatoid arthritis	37
---	----

Classification of rheumatoid arthritis	40
--	----

Management of early rheumatoid arthritis	40
--	----

Recommendations for the management of early rheumatoid arthritis	44
--	----

References	63
------------	----

4	Established rheumatoid arthritis	67
	Introduction	67
	Stages of established rheumatoid arthritis	69
	Common clinical presentations	72
	References	88
5	Remission and rheumatoid arthritis	89
	Introduction	89
	Defining remission	90
	Imaging remission	92
	Immune-mediated remission	95
	Drug-free remission	96
	Optimal dose reduction regimes for patients in remission	98
	References	117
	PART TWO IMAGING OF RHEUMATOID ARTHRITIS	
6	Magnetic resonance imaging in rheumatoid arthritis	123
	Introduction	123
	Technical aspects	123
	Visualizing rheumatoid arthritis	124
	Diagnosing rheumatoid arthritis	125
	Monitoring disease activity and structural damage	126
	References	136

7	Ultrasound imaging in rheumatoid arthritis	139
	Introduction	139
	Ultrasound and rheumatoid arthritis	140
	Cartilage damage	142
	Management of rheumatoid arthritis with ultrasound: diagnosis, therapeutic follow-up, remission, and flare	142
	Conclusion	143
	References	151
8	Dual energy X-ray absorptiometry in rheumatoid arthritis	155
	Introduction	155
	Bone remodeling in rheumatoid arthritis	155
	Bone damage imaging in rheumatoid arthritis	156
	Treatment of bone loss in rheumatoid arthritis	159
	References	170
	PART THREE TREATMENT OF RHEUMATOID ARTHRITIS	
9	Methotrexate	175
	Introduction	175
	Historical perspective	175
	Mechanism of action and pharmacokinetics	176
	Dosing	177
	Benefits	177

Monitoring	178
References	190
10 Immunotherapy	193
Introduction	193
Nonbiologic disease-modifying antirheumatic drugs	194
Biologic disease-modifying antirheumatic drugs	196
Cost-effectiveness of immunotherapy in early rheumatoid arthritis	202
Recommendations for the use of disease-modifying antirheumatic drug therapies	203
Safety of immunotherapy	204
Prospective new targets for immunotherapy	205
References	225
11 Rituximab	231
B-cell development and differentiation	231
Efficacy of rituximab in rheumatoid arthritis	232
References	246
12 Novel therapies in rheumatoid arthritis: small molecules	249
Introduction	249
Inhibiting intracellular signaling pathways	252
Conclusion	255
References	263

Contributors

Graciela S Alarcón

Division of Clinical Immunology
and Rheumatology
University of Alabama at Birmingham
Birmingham, Alabama, USA

Daniel Aletaha

Division of Rheumatology
Department of Internal Medicine
Medical University of Vienna
Vienna, Austria

Mette Bjørndal Axelsen

Copenhagen Center for Arthritis
Research
Copenhagen University Hospital
Glostrup, Denmark

Mikael Boesen

Department of Rheumatology
The Parker Institute
Copenhagen University Hospital
Copenhagen, Denmark

Maya H Buch

Leeds Institute of Rheumatic and
Musculoskeletal Medicine University
of Leeds; NIHR Leeds Musculoskeletal
Biomedical Research Unit, Leeds
Teaching Hospitals NHS Trust
Leeds, UK

Maria Antonietta D'Agostino

Department of Rheumatology
Ambroise Paré Hospital
University Paris Ouest-Versailles-Saint-
Quentin-en-Yvelines
Boulogne-Billancourt, France

Atul Deodhar

Division of Arthritis & Rheumatic
Diseases
Oregon Health & Science University
Portland, Oregon, USA

Sarah C Horton

Leeds Institute of Rheumatic and
Musculoskeletal Medicine University
of Leeds; NIHR Leeds Musculoskeletal
Biomedical Research Unit, Leeds
Teaching Hospitals NHS Trust
Leeds, UK

Tom WJ Huizinga

Department of Rheumatology
Leiden University Medical Center
Leiden, The Netherlands

Thomas J Learch

Division of Imaging
Cedars-Sinai Medical Center
Los Angeles, California, USA

Jackie L Nam

Leeds Institute of Rheumatic and
Musculoskeletal Medicine University
of Leeds; NIHR Leeds Musculoskeletal
Biomedical Research Unit, Leeds
Teaching Hospitals NHS Trust
Leeds, UK

Mikkel Østergaard

Copenhagen Center for Arthritis
Research
Copenhagen University Hospital
Glostrup, Denmark

Monique Reijnerse

Department of Rheumatology
Leiden University Medical Center
Leiden, The Netherlands

Benazir Saleem

Rheumatology Department
York Teaching Hospitals NHS Trust
York, UK

David Sandoval

Seattle, Washington, USA

Josef S Smolen

Department of Rheumatology
Medical University of Vienna
Vienna, Austria

Wouter Stomp

Department of Rheumatology Leiden
University
Medical Center
Leiden, The Netherlands

Michael H Weisman

Division of Rheumatology
Cedars-Sinai Medical Center
Los Angeles, California, USA

**Annette HM van der Helm-
van Mil**

Department of Rheumatology
Leiden University
Medical Center
Leiden, The Netherlands

Ed Vital

Leeds Institute of Rheumatic and
Musculoskeletal Medicine University
of Leeds; NIHR Leeds Musculoskeletal
Biomedical Research Unit, Leeds
Teaching Hospitals NHS Trust
Leeds, UK

Editor biography

Professor Paul Emery is the Arthritis Research UK Professor of Rheumatology and Director of the Leeds Institute of Rheumatic and Musculoskeletal Medicine and the Director of the Leeds Musculoskeletal Biomedical Research Unit at Leeds Teaching Hospitals Trust in Leeds, United Kingdom. Professor Emery was the President of the European League Against Rheumatism (EULAR) from 2009–2011 and has served on the editorial boards major rheumatology journals including Rheumatology, Arthritis and Rheumatism, Annals of the Rheumatic Diseases, Clinical and Experimental Rheumatology, and Clinical Rheumatology. He was the inaugural President of International Extremity MRI Society (ISEMIR) and is a National Institute for Health Research (NIHR) Senior Investigator. Professor Emery is a recipient of the Roche Biennial Award for Clinical Rheumatology; the Rheumatology Hospital Doctor of the Year Award; the EULAR Prize for outstanding contribution to rheumatology research; and the Carol Nachman Prize for outstanding rheumatology research. Professor Emery's research interests center around the immunopathogenesis and immunotherapy of rheumatoid arthritis, spondyloarthritis, and connective tissue diseases. He has a special interest in the factors leading to persistent inflammation and has published over 950 peer-reviewed articles in this area.

Rheumatoid arthritis overview

1 Classification of rheumatoid arthritis

Daniel Aletaha

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects approximately 1% of the adult population [1]. Although there is no cure, patients may reach a state of remission, which has become an achievable goal with optimal early treatment. Early intervention in particular has made RA a less disabling disease and if treatment is instituted right from the onset, no functional impairment may occur and structural integrity may be preserved (Figures 1.1 and 1.2) [2]. Over the past decade, early intensive treatment has also been proven to change the course of later RA [2,3], and therefore, the treatment goal should be to treat RA early and persistently until remission is present [4,5].

The challenge of treating early RA is the fact that new-onset arthritis often resolves spontaneously and persistent arthritis has many differential diagnoses to be considered in addition to RA, or may even remain undifferentiated (Figure 1.3). Diagnostic algorithms have been suggested for new-onset arthritis, as there is minimal work-up needed to label the presentation as undifferentiated (Figure 1.4) [6]. Algorithms also help with the exclusion of trauma, gout, and septic arthritis; suspicion of one of the latter two requires joint fluid aspiration, which usually gives immediate diagnostic clues (Figure 1.5).

In the early treatment of RA, there are many hurdles that can cause a substantial delay in beginning treatment, including delays in patient presentation, physician referral, or diagnosis (Figure 1.6) [7]. In most clinical settings, a diagnosis will need to be established before medication can be

instituted, including liability considerations with the use of off-label drugs. Because diagnostic criteria are not available, the diagnosis will have to be established by the rheumatologist, although he or she may decide to use a formal classification system as a basis (Figure 1.7).

The 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria were developed in a three-stage process (Tables 1.1 and 1.2; Figures 1.8 to 1.10) to replace existing criteria, which were deemed out of date [8,9]. The 2010 ACR/EULAR criteria comprise a scoring system that considers the number and distribution of the affected joints, serology, duration of symptoms, and acute phase reactants (Table 1.3) [10]. They may be applied to patients with clinical arthritis, in whom another disease can be reasonably excluded (Figure 1.11), and may be applied prospectively or retrospectively (Figure 1.12). In addition to the direct scoring system, a tree algorithm has also been provided, the result of which is identical to the scoring system (Figure 1.13) [10]. Because the new criteria do not factor in joint erosion, which is now considered more a preventable outcome of RA rather than a classification marker, additional rules have been defined for patients who present with available X-rays of their hands and feet (Figure 1.14).

In summary, making a correct diagnosis of RA (especially early RA) remains a challenge. Because there are a large number of differential diagnoses, and the presentation of RA may be considerably heterogeneous, no formal criteria can replace the judgment and experience of the rheumatologist in the diagnostic setting. Nevertheless, classification criteria may help to guide the rheumatologist in the difficult task of establishing a diagnosis. This will allow early institution of adequate therapy and, hopefully, help to reduce the impact of this very prevalent disease on patient function and health-related quality of life.

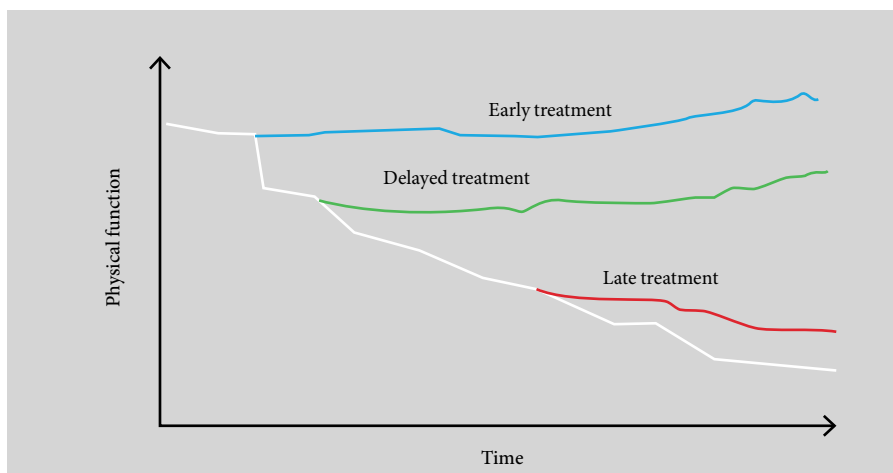


Figure 1.1 Why is early classification of rheumatoid arthritis needed? Over time, structural damage increases and physical function declines if rheumatoid arthritis (RA) is not treated effectively. While institution of therapy in late RA can improve function to only a very small extent, earlier treatment has the potential to stabilize physical function before permanent disability occurs.

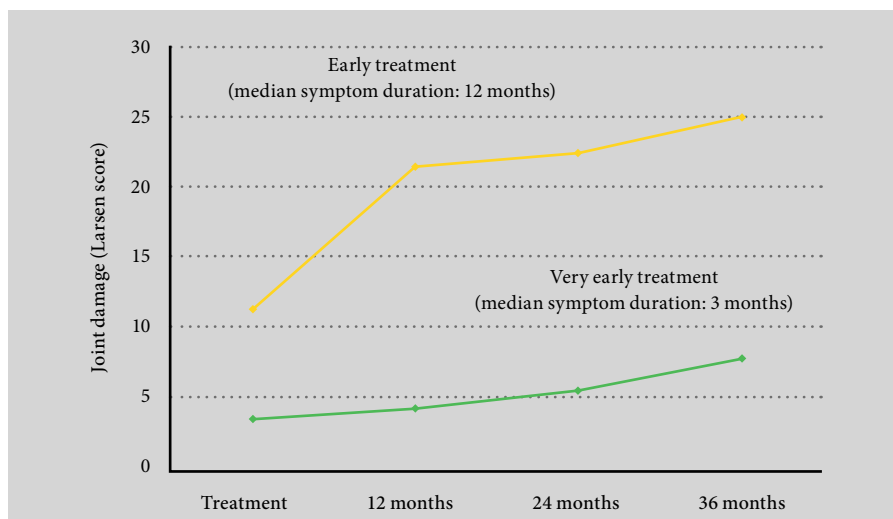


Figure 1.2 The importance of starting rheumatoid arthritis therapy very early. Even short delays in treatment initiation in patients with rheumatoid arthritis (RA) can lead to a considerable increase in structural damage over the course of 3 years. The yellow line shows that progression in Larson radiographic scores is already substantial in patients receiving early treatment initiation (ie, with a median symptom duration of only 12 months). In very early treatment initiation (ie, with a median symptom duration of 3 months, as represented by the course of the green line), the slope of progression is flattened and after 3 years, these patients did not reach the degree of structural damage that the early treatment initiation group already had at baseline despite only a 9-month delay in treatment. Adapted with permission from Nell et al [2] ©Oxford University Press.

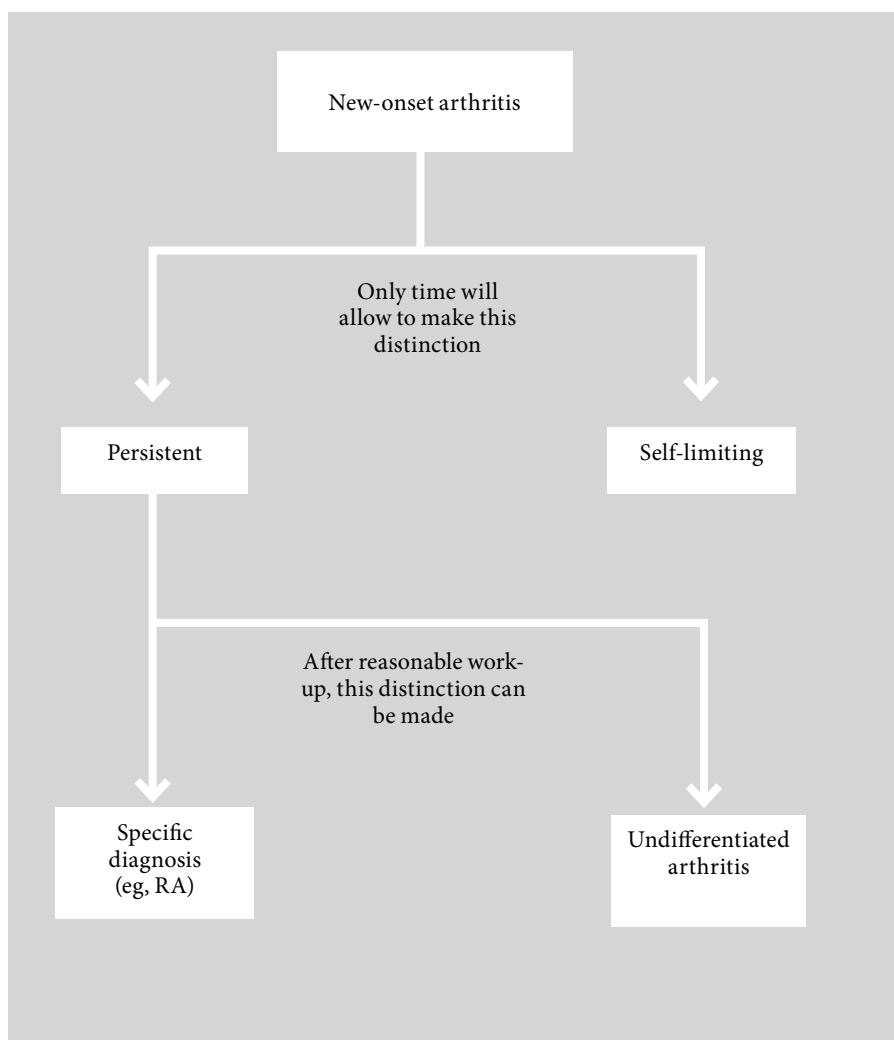


Figure 1.3 From symptom to diagnosis: rheumatoid arthritis. New-onset arthritis can have numerous causes. Only time will allow for a distinction between a self-limiting and a persistent disease. A reasonable clinical work-up needs to be done to be able to label arthritis as 'undifferentiated,' if a specific diagnosis cannot be established otherwise. RA, rheumatoid arthritis.

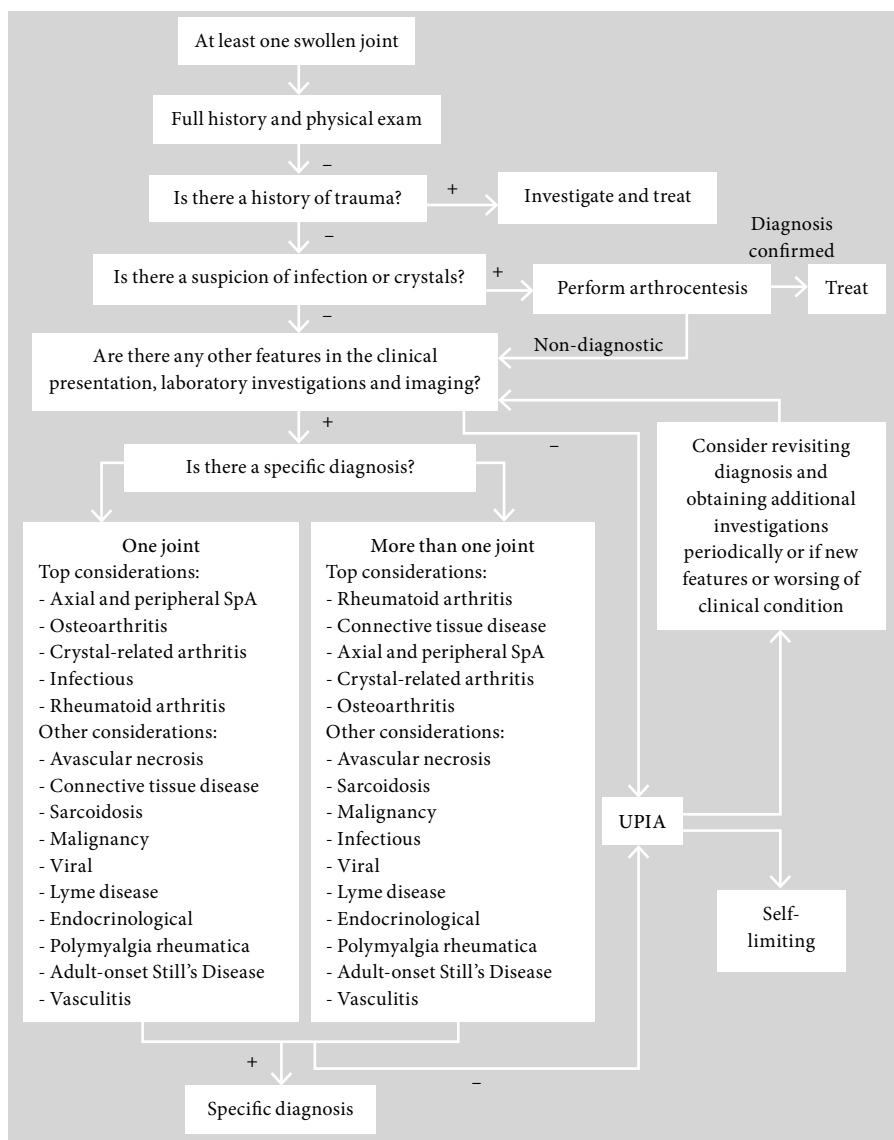


Figure 1.4 Flowchart for establishing a specific diagnosis in new onset arthritis in at least one swollen joint. Starting point in rheumatoid arthritis diagnosis is a full health history and physical examination. After exclusion of trauma and acute inflammatory events, a specific diagnosis may be established in the presence of suggestive clinical, laboratory, or imaging features, where the differential diagnoses vary according to the number of swollen joints involved. If no specific diagnosis can be established, the presentation may be labeled as 'undifferentiated arthritis' (or undifferentiated peripheral inflammatory arthritis). This status needs to be re-evaluated periodically, as undifferentiated arthritis may evolve into a specific diagnosis over time. SpA, spondyloarthritis; UPIA, undifferentiated peripheral inflammatory arthritis. Adapted with permission from Hazelwood et al [6] ©Journal of Rheumatology.

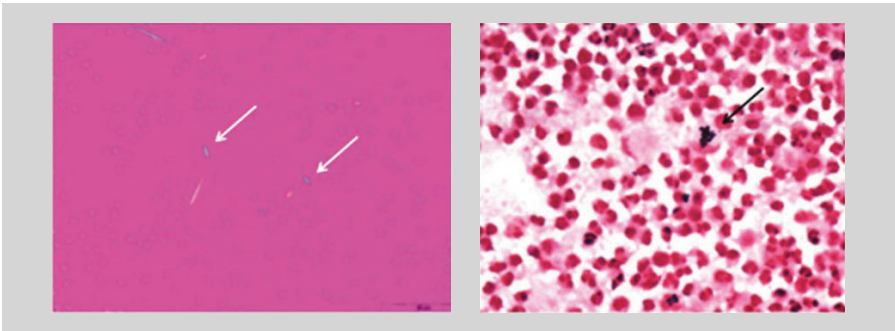


Figure 1.5 Microscopic synovial fluid analysis. Left panel: Crystal arthritis – evidence of intracellular needle shaped crystals (white arrows). Right panel: Septic arthritis showing positive Gram stain of cocci (*Staphylococcus aureus*) in typical formation (black arrow). Photo courtesy of Professor Stefan Winkler, Division of Infectious Diseases, Medical University Vienna, Austria.

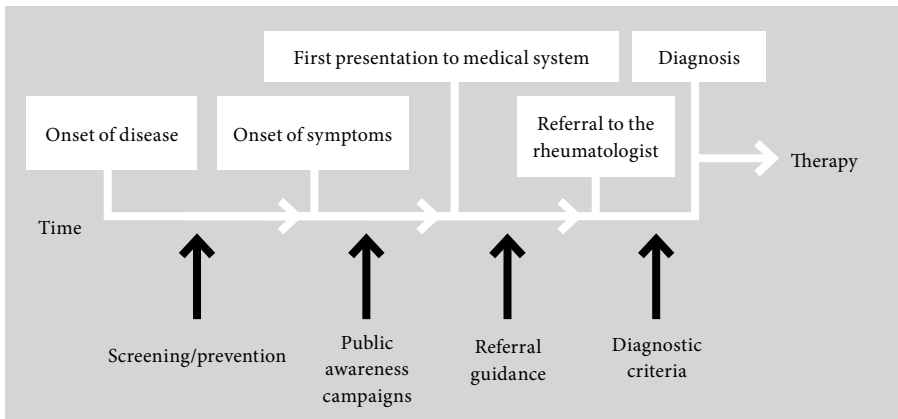


Figure 1.6 Limiting factors of early treatment. Several types of delays can occur in the course of arthritis diagnosis and treatment. First, there can be a delay between disease onset and the onset of symptoms, where screening methods (in the future) may be able to elicit preventive means. It takes varying periods of time until patients present symptoms to a medical professional, usually to a general practitioner (GP), who then may take some time before referring a patient to a rheumatologist. Greater public awareness can shorten the former, and referral guidance may be provided to GPs to shorten the latter. It may also take time until the rheumatologist has established a diagnosis. Unfortunately, no diagnostic criteria are available for rheumatoid arthritis, and this will likely not change in the future due to the complex nature of the disease. Therefore, classification criteria are often used to inform the clinical diagnosis, although their purpose is different. Adapted with permission from Aletaha and Huizinga [7] ©Elsevier.

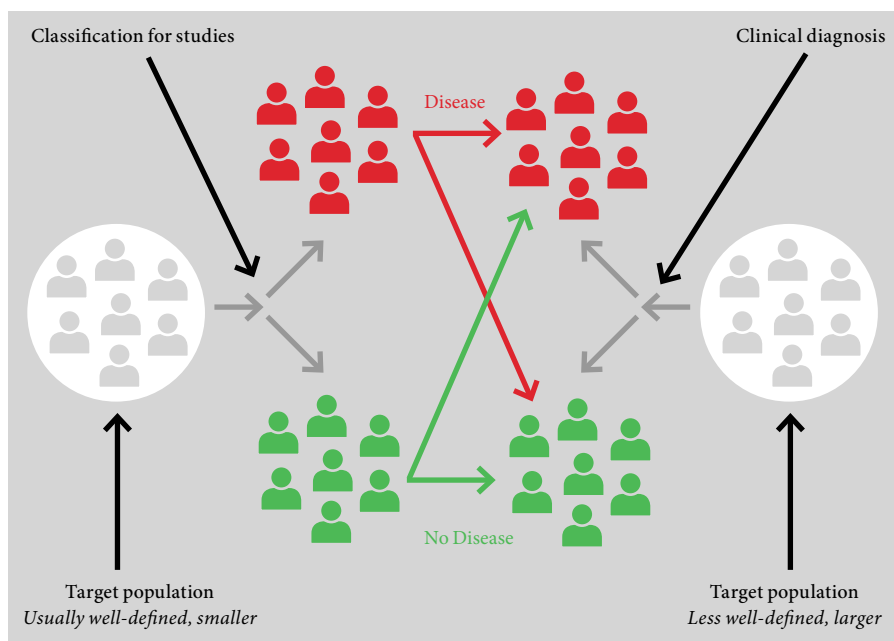


Figure 1.7 Differences between classification and diagnosis of disease. Classification criteria are developed for the purpose of identifying a homogeneous group of individuals for enrollment in clinical studies (eg, trials, observational studies, surveys). Individuals tested with classification criteria are usually well-defined. In contrast, a diagnosis has to be established by the rheumatologist and criteria are missing for most diseases. The target population for diagnosis is much wider and much more heterogeneous. Diagnostic criteria would need to be tested in various clinical settings (to patient groups with different background probabilities of disease) to understand their specific interpretation. Clinicians may adopt classification criteria to inform their diagnosis, but they will need to be aware that a classification incorporates the risk of a false-positive or false-negative, and relates to a specific (predefined) target population. In several instances, the result of the classification criteria will thus need to be overruled by the clinician.

Factor	Loading variables	Theme	Represented by
1	SJC, MCP _{SW} , MCP _{SW-Sym}	'MCP involvement'	MCP swelling (SW)
2	Wrist _{SW} , Wrist _{TD} , Wrist _{SW-Sym}	'Wrist involvement'	Wrist swelling
3	Tender joint count, MCP _{TD} , PIP _{TD}	'Hand/finger tenderness'	PIP or MCP or wrist tenderness (TD)
4	CRP, ESR	'Acute phase response'	Abnormal CRP or abnormal ESR
5	PIP _{SW} , PIP _{TD}	'PIP involvement'	PIP swelling
6	ACPA-positive, RF-positive	'Serology'	Positive for ACPA or RF

Table 1.1 Results of the data-driven Phase 1 of the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria: identifying variables important for classification of rheumatoid arthritis. After univariate analysis of candidate variables for prediction of methotrexate initiation, six predicting factors were determined by using principal component analysis (metacarpophalangeal joint involvement, wrist involvement, tenderness of the hand, acute phase response, proximal interphalangeal joint involvement, serology). Based on the loading of individual variables on these factors, each factor was attributed a theme. Subsequently, the most representative variable for each factor (and the most feasible) was then selected for further analysis in a multivariate model. ACPA, antibodies against citrullinated peptides; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MCP, metacarpophalangeal; PIP, proximal interphalangeal; RF, rheumatoid factor. Adapted with permission from Funovits et al [8] ©BMJ.

Representing variable	Comparison	P-value	OR (95% CI)	Weight
Swollen MCP	Present vs. absent	0.003	1.46 (1.14 to 1.88)	1.5
Swollen PIP	Present vs. absent	0.001	1.51 (1.19 to 1.91)	1.5
Swollen wrist	Present vs. absent	<0.001	1.61 (1.28 to 2.02)	1.5
Hand tenderness	Present vs. absent	<0.001	1.80 (1.33 to 2.44)	2
Acute phase	Moderate vs. normal	0.172	1.24 (0.91 to 1.70)	1
	High vs. normal	0.001	1.68 (1.23 to 2.28)	2
Serology	Moderate vs. normal	<0.001	2.22 (1.81 to 3.28)	2
	High vs. normal	<0.001	3.85 (2.96 to 5.00)	4

Table 1.2 Results of the data driven phase 1 of the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification project: analysis of independent contributions of important variables. The six variables representing each of the themes identified through univariate analysis and variable loading (metacarpophalangeal joint involvement, MCP, wrist involvement, tenderness of the hand, acute phase response, proximal interphalangeal joint involvement, PIP, serology) were tested in the depicted multivariate logistic regression model, using methotrexate treatment at 1 year after presentation as the reference standard. The odds ratios (ORs), refer to the independent contribution to the risk of methotrexate treatment, and the weight is based on the respective odds ratios estimated by the model. Adapted with permission from Funovits et al [8].

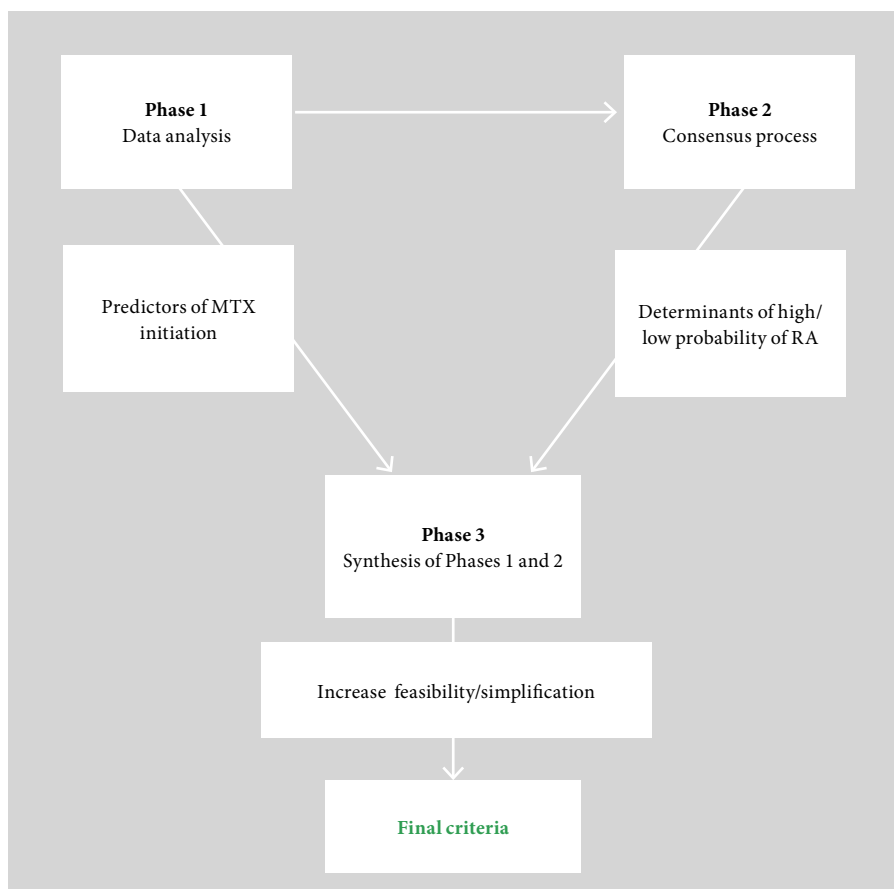


Figure 1.8 Schematic of the process to develop new classification criteria for rheumatoid arthritis. The 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria were derived in a three-stage process. Initially, a data analysis of several early arthritis cohorts, mostly from Europe, was used to identify the best predictors for treatment with methotrexate (MTX), which was deemed to be the best possible indicator of the physician's belief that this presentation was developing into the chronic, erosive rheumatoid arthritis (RA). During the second phase, a consensus process using conjoint decision analysis took place that fruited in the identification of determinants of a high probability of RA from the expert clinician's perspective. The results were synthesized in the last phase to increase practical usability and feasibility of the criteria in their application.

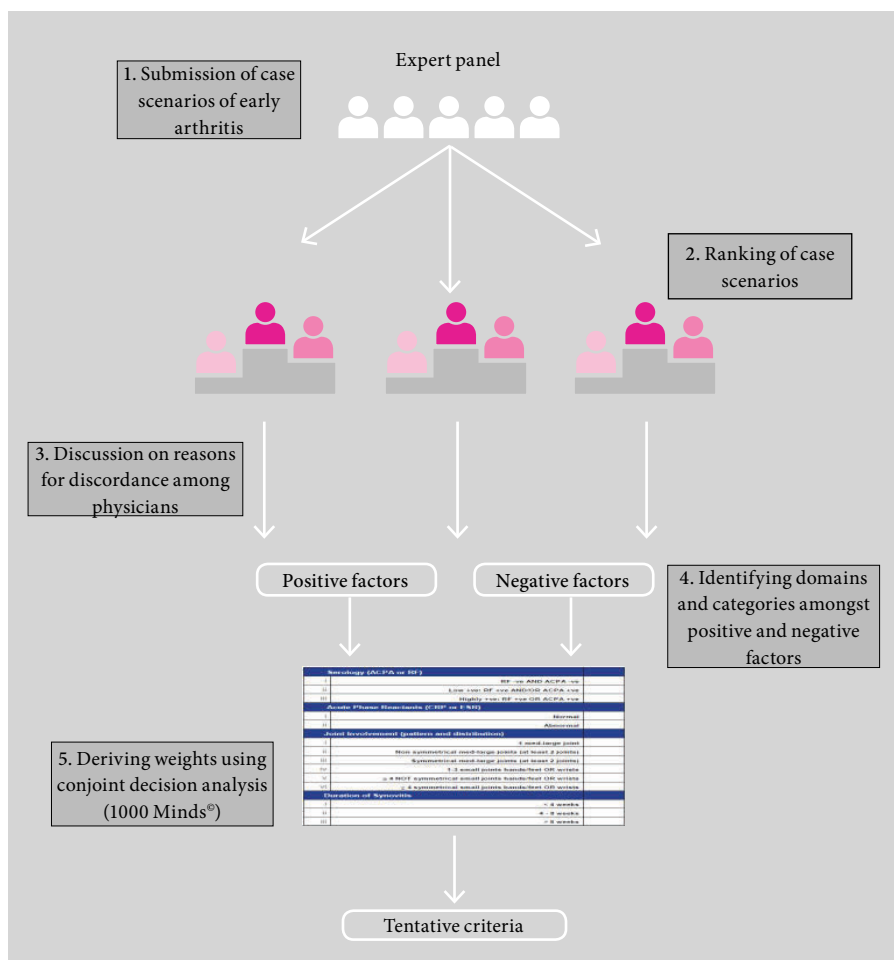


Figure 1.9 Overview of Phase 2 of the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for rheumatoid arthritis. 1. A panel of 24 international experts was established, each of whom submitted a number of case scenarios on early arthritis patients. 2. A selection of 30 heterogeneous scenarios were then ranked by the experts for their probability of developing rheumatoid arthritis (RA). These rankings were very heterogeneous and showed a high level of discordancy across the experts. 3. The results were then discussed to understand its reasons and causes for such discrepancy across the experts. This included possible features in the presentation that guided an expert towards choosing a higher probability ('positive factors') or lower probability ('negative factors'). 4. Domains were identified for all positive and negative factors, and categories were defined within each domain. 5. A computer-assisted decision analysis exercise was performed in which each category within each domain was assigned a specific weight, reflecting how strongly it affects the probability of developing RA from the perspective of expert clinicians. This led to the tentative criteria in Phase 2, which were then used to develop the final criteria set.

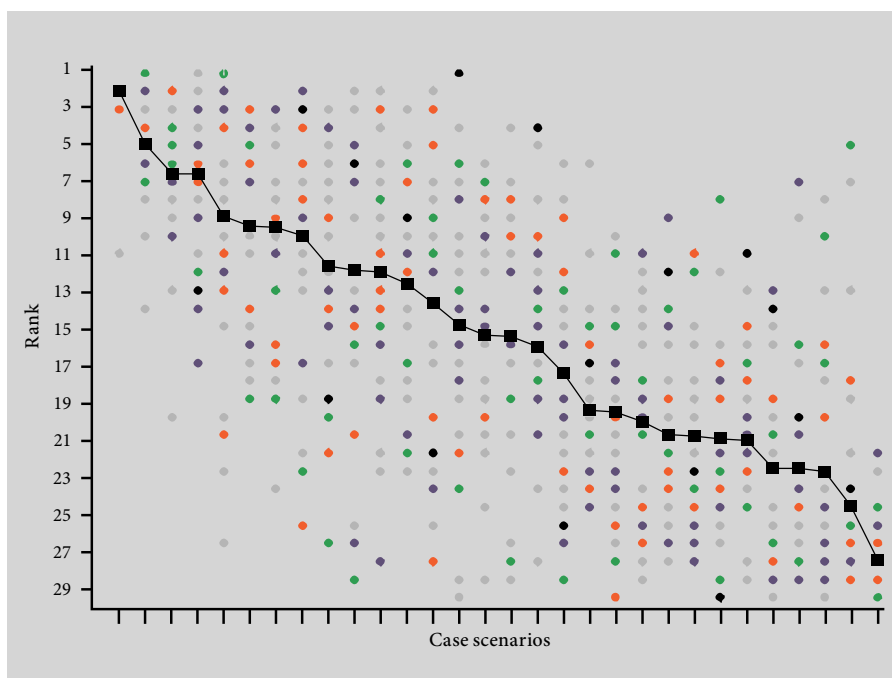


Figure 1.10 Discordance of expert clinicians in a ranking exercise of arthritis cases by their probability to develop rheumatoid arthritis. The vertical axis depicts the rank allocation (1–30) by each of the 24 experts (represented by differently colored dots) across the 30 selected case scenarios represented on the horizontal line (ordered by their average rank, from left to right; black marks and black connecting line). It can be seen that only in a few cases experts had consistent views (ie, left-most and right-most cases). All other cases showed substantial spread of rank allocations by different experts. The discussion of the reasons for discordance within these rankings led to the identification of important domains for the classification criteria from the clinical perspective. Reproduced with permission from Neogi et al [9] ©BMJ.

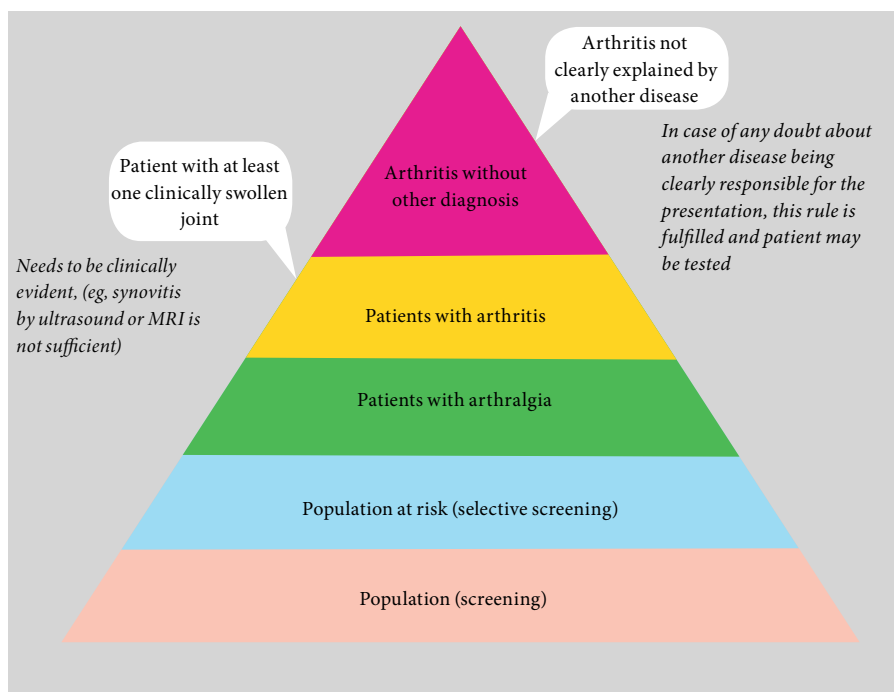


Figure 1.11 The target population for the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for rheumatoid arthritis. The criteria may not be applied for population screening of rheumatoid arthritis (RA) or screening of individuals at risk of RA (eg, those with a positive family history of RA), nor for individuals with mere arthralgia. The requirements for patients to be tested with the criteria are (1) clinically evident arthritis (eg, joint swelling, synovitis); and (2) absence of evidence of another entity that clearly better explains the presentation (eg, acute gout attack).

Joint distribution (0–5 points)	Points
Joint involvement: Any swollen or tender joint (excluding DIP of hand and feet, 1st MTP, 1st CMC) Additional evidence from MRI/ultrasound may be used to identify additional joints	
• 1 large joint (shoulder, elbow, hip, knee, ankles)	0
• 2–10 large joints	1
• 1–3 small joints (MCP, PIP, MTP 2–5, thumb IP, wrist); large joints not counted Does not include: DIP, 1st CMC, 1st MTP	2
• 4–10 small joints (large joints not counted)	3
• <10 joints (at least one small joint) Additional joints include: temporomandibular, sternoclavicular, acromioclavicular, and others (as reasonably expected in RA)	5
Serology (0–3 points)	
Serology: Negative: $\leq$ ULN (for the respective lab) Low positive: $>$ ULN but $\leq 3 \times$ ULN High positive: $> 3 \times$ ULN <i>Where RF is only available qualitatively, a positive result should be scored as 'low-positive' for RF</i>	
Negative RF AND negative ACPA	0
Low positive RF OR low positive ACPA	2
High positive RF OR high positive ACPA	3
Symptom duration (0–1 points)	
Symptom duration: Refers to the patient's self-report on the maximum duration of signs and symptoms of any joint that is clinically involved at the time of assessment.	
<6 weeks	0
≥ 6 weeks	1
Acute phase reactants (0–1 points)	
Normal CRP AND ESR	0
Abnormal CRP OR abnormal ESR <i>Normal/abnormal ESR/CRP is determined by local laboratory standards</i>	1
Score ≥ 6 = Classification of RA	TOTAL:

Table 1.3 The 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for rheumatoid arthritis. A score of 6/10 needs to be achieved from four domains including: joint activity (0–5 points), serology (0–3 points), symptom duration (0–1 point), and acute phase response (0–1 point). ACPA, anti-citrullinated protein/peptide antibodies; CRP, C-reactive protein; DIP, distal interphalangeal; ESR, erythrocyte sedimentation rate; MCP, metacarpophalangeal; MTP, metatarsophalangeal; RF, rheumatoid factor; ULN, upper limit of normal. Adapted with permission from Aletaha et al [10]©BMJ.

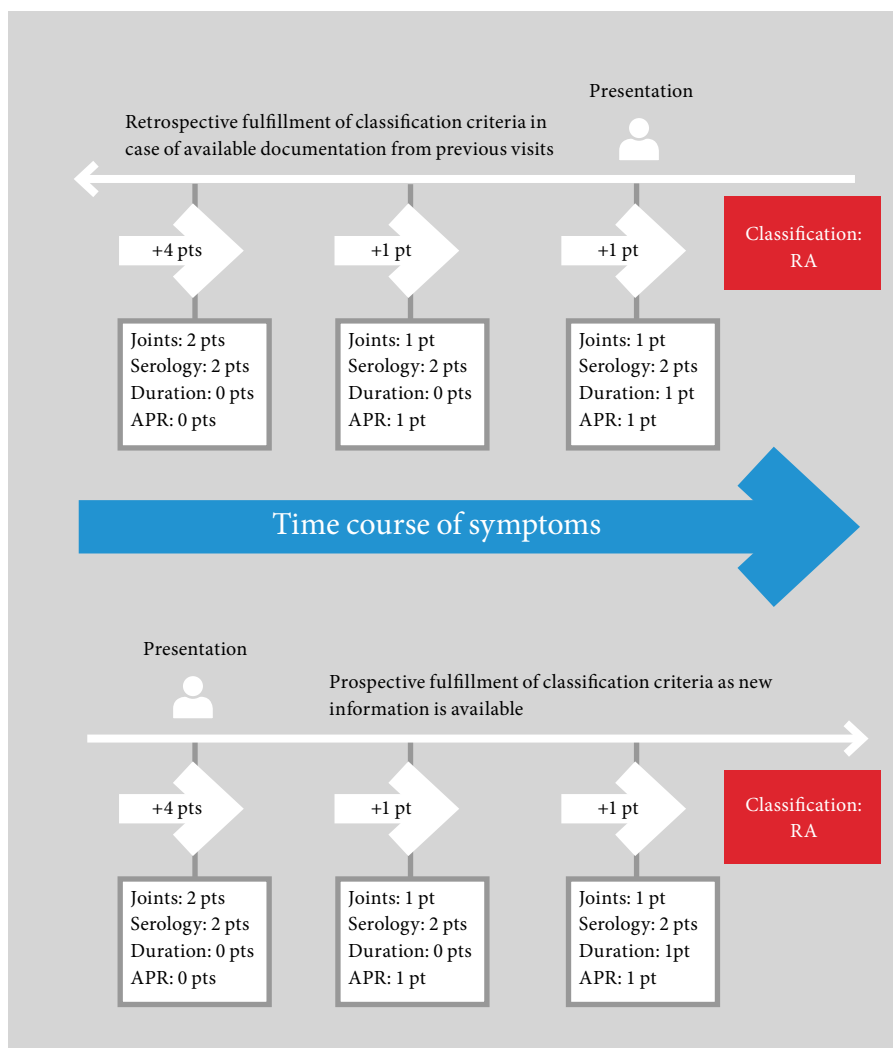
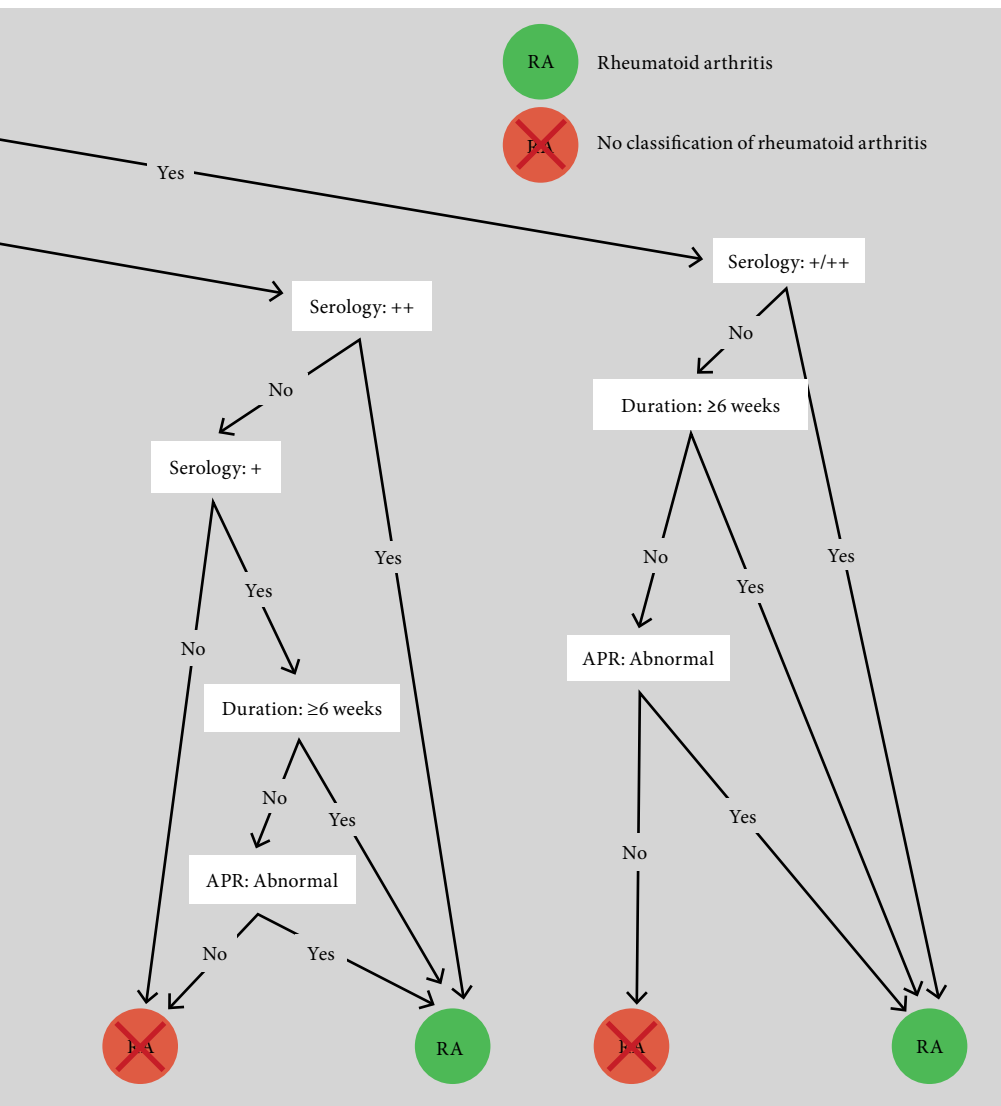


Figure 1.12 Cumulative fulfillment of the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for rheumatoid arthritis. The criteria may be fulfilled cumulatively over time, either retrospectively or prospectively. If a patient presents with a reasonable documentation on any of the domains represented in the criteria, then these can be counted towards a classification. Similarly, points in the classification system may also be collected over several prospective visits. Even if previous symptoms change, the highest score within each domain may be retained and used. APR, acute phase response; RA, rheumatoid arthritis.



Figure 1.13 Tree algorithm for classification of rheumatoid arthritis (RA; green circles) or to exclude its current presence (red circles). The starting point is an eligible patient with clinical synovitis, in whom no other diagnosis clearly better explains the presentation. Definitions used in the algorithm are consistent with the scoring system. Serology includes rheumatoid factor (RF) or anti-citrullinated protein/peptide antibodies (ACPA); + refers to low-positive levels (ie, IU values that are greater than the upper limit of normal [ULN], but $\leq 3 \times \text{ULN}$ for the lab and assay) for at least one of them; ++ refers to high-positive values (IU values that are $> 3 \times \text{ULN}$) for at least one. Acute phase response includes erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP); normal/abnormal ESR/CRP are determined by local laboratory standards. Duration refers to patient self-report of the duration of signs or symptoms of synovitis (eg, pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status. CMC, carpometacarpal joint; DIP, distant interphalangeal joint; MCP,



metacarpophalangeal joint; MTP, metatarsophalangeal joints; PIP, proximal interphalangeal joint. Adapted with permission from Aletaha et al [10] ©BMJ.

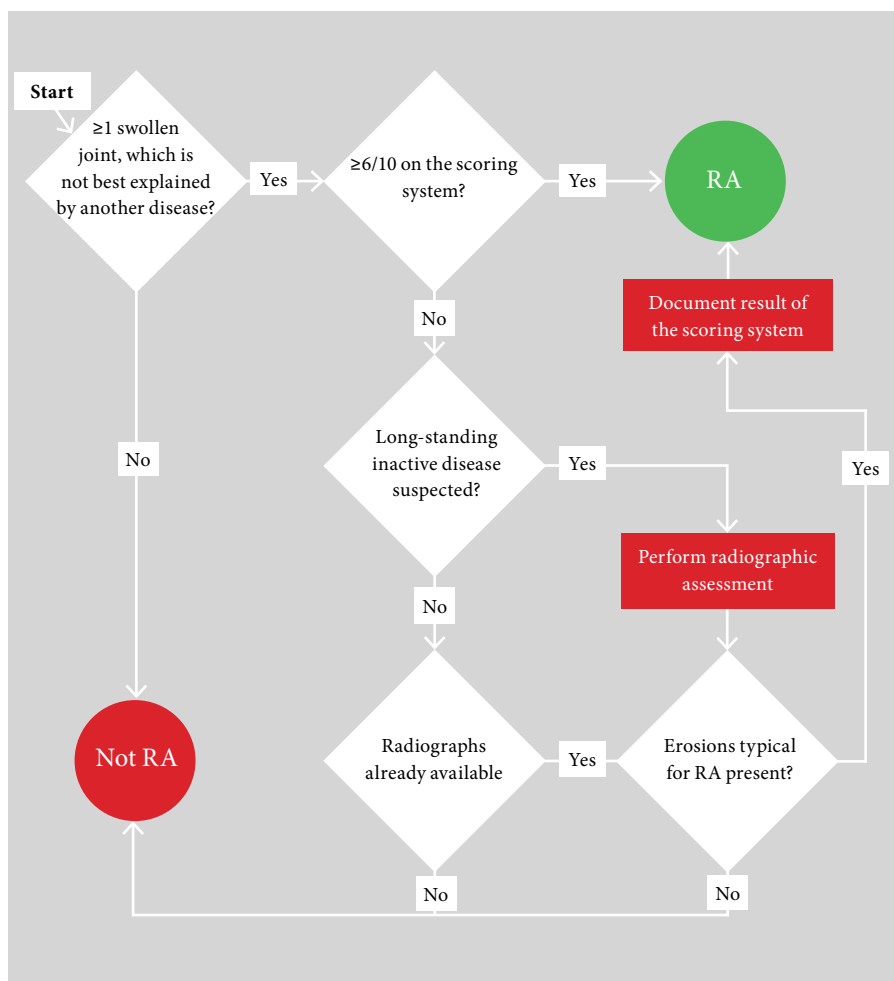


Figure 1.14 Consideration of radiographic evidence of rheumatoid arthritis in the context of the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria. Radiographic damage is not a core criterion of the classification system, as mostly classification takes place at an early stage of the disease. In the rare instances where it is clinically suspected that long-standing inactive disease is present (eg, by the presence of deformities), and classification has never been attempted, radiographic evidence of erosions typical for rheumatoid arthritis (RA) may be used to directly classify patients. The same would apply for typical (ie, not long-standing) patients who present with a recent radiograph of their hands. In this situation, the information should not be ignored, and in the rare occasions that non-long-standing patients who failed to classify the scoring system, show erosive disease typical of RA, a classification would be possible.

References

1. Kvien TK. Epidemiology and burden of illness of rheumatoid arthritis. *Pharmacoeconomics*. 2004;22(2 suppl):1-12.
2. Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS. Benefit of very early referral and very early therapy with disease-modifying antirheumatic drugs in patients with early rheumatoid arthritis. *Rheumatology (Oxford)*. 2004;43:906-914.
3. Landewe RB, Boers M, Verhoeven AC, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. *Arthritis Rheum*. 2002;46:347-356.
4. Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis*. 2010;69:631-637.
5. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis*. 2010;69:964-975.
6. Hazlewood G, Aletaha D, Carmona L, et al. Algorithm for identification of undifferentiated peripheral inflammatory arthritis: a multinational collaboration through the 3e initiative. *J Rheumatol Suppl*. 2011;87:54-58.
7. Aletaha D, Huizinga TW. The use of data from early arthritis clinics for clinical research. *Best Pract Res Clin Rheumatol*. 2009;23:117-123.
8. Funovits J, Aletaha D, Bykerk V, et al. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: methodological report phase I. *Ann Rheum Dis*. 2010;69:1589-1595.
9. Neogi T, Aletaha D, Silman AJ, et al. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: Phase 2 methodological report. *Arthritis Rheum*. 2010;62:2582-2591.
10. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis*. 2010;69:1580-1588.

2 Pre-rheumatoid arthritis

Annette HM van der Helm-van Mil, Wouter Stomp,
Monique Reijnders, Tom WJ Huizinga

What is pre-rheumatoid arthritis?

In recent years, research in the field of rheumatoid arthritis (RA) has focused on the earliest stages of disease. Different terminologies for pre-clinical and very early clinical disease stages are used; ‘pre-RA’ is one of these terms. In order to facilitate communication, a European League Against Rheumatism (EULAR) task force has derived recommendations for terminology to be used during the preclinical and earliest clinically apparent phases of RA. The following phases in the development of RA were described (Figure 2.1) [1]:

- genetic risk factors;
- environmental risk factors;
- systemic autoimmunity;
- symptoms without clinical arthritis;
- unclassified arthritis (UA); and
- RA.

Importantly, not every patient has to experience each stage and the phases can be used in a combinatorial manner. For instance, a patient can have genetic risk factors, anticyclic citrullinated peptide antibodies (ACPA), and arthralgia. In this chapter, the presently available knowledge on these specific phases has been summarized.

Risk factors for rheumatoid arthritis

Genetic risk factors

At present, more than 100 genetic risk factors for RA have been identified and replicated (Table 2.1). The majority of these risk factors have a moderate

minor allele frequency. This indicates that the risk alleles are not rare but are quite commonly present in the population. In contrast to the prevalence of these risk factors, the odds ratios are relatively small (in the range of 1.1–1.3). This indicates that carrying a single risk factor does not yield a dramatically increased risk of RA. Interestingly, several of the identified genes lie on the same pathway. For example, HLA class II histocompatibility antigen DRB1-9 beta chain (*HLA-DRB1*), protein tyrosine phosphatase non-receptor type 22 (*PTPN22*), signal transducer and activator of transcription 4 (*STAT4*), cluster of differentiation 40 (*CD40*), cytotoxic T-lymphocyte antigen 4 (*CTLA4*), interleukin (*IL*)2, *IL21*, and protein kinase C theta type (*PRKCQ*) are all involved in T-cell activation, while *CD40*, *CTLA4*, *IL 2*, *IL21*, *PRKCQ*, *PTPN22*, *STAT4*, tumor necrosis factor alpha-induced protein 3 (*TNFAIP3*), and tumor necrosis factor receptor-associated factor 1 (*TRAF1*) are involved in cell-cycle regulation.

Importantly, the majority of the genetic risk factors are identified in ACPA-positive RA. It is suggested that ACPA-positive and ACPA-negative RA have dissimilar genetic risk factors but the heritability of both subgroups is similar (66% and 68%, respectively) [2]. This implies that the majority of genetic risk factors for ACPA-negative RA are as yet unidentified. Moreover, in ACPA-positive RA, the known risk factors do not explain the total genetic contribution to RA, suggesting that other genetic factors play a role as well. Therefore, more current ongoing genetic studies focus on rare genetic variants. Although these will be less common, it is expected that these variants will have a higher effect size. At the time of writing, no large-scale sequencing studies in patients with RA have been published.

Environmental risk factors

The known environmental risk factors for RA are summarized in Table 2.2 [3–16]. Given a heritability of 66%, up to 34% of the variance may be explained by environmental factors. Smoking is the only environmental factor that is widely replicated as a risk factor, particularly in persons that carry *HLA-DRB1* shared epitope alleles [6].

Systemic autoimmunity associated with rheumatoid arthritis

When examining serum of patients with RA that was collected before their arthritis became clinically apparent, a proportion of these patients had detectable rheumatoid factor (RF) or ACPA in the years before the development of arthritis (Figure 2.2) and the maturation of this auto-antibody response has taken place in the preclinical phase [9]. Similarly, acute phase reactants and bone degradation products have been found to be present in the phase before

arthritis occurs (Table 2.3) [17–23]. Together these data suggest that in patients with RA, the onset of the disease preceded the onset of clinically detectable arthritis. Although these data are highly interesting, prospective data are still scarce, leaving the question of what proportion of ACPA-positive persons in the general population will develop RA unanswered.

Symptoms without clinical arthritis

Symptoms that are specific for developing arthritis have not been explicitly described by the EULAR task force. From a clinical perspective, such information would be highly relevant, though at present data are scarce on this issue. The majority of existing data originate from cohorts in the Netherlands and Sweden [24,25]. In the Dutch cohort, it was observed that from a population of patients who were ACPA-positive with arthralgia, 20% developed RA; whereas from all patients who were ACPA-positive with symmetric arthralgia of small joints, 60% developed RA [24]. Because, clinically, there is no local inflammation detectable in this phase, the question is whether local subclinical inflammation can be detected in this phase using imaging techniques. Ultrasound was performed in the Dutch study; at a patient level, there were no significant differences in joint effusion, synovitis, or Power Doppler signals between those who did and did not develop RA [25]. In another study, patients who were auto-antibody-positive had magnetic resonance imaging (MRI) and an arthroscopic synovial biopsy on their knee joints, also revealing no subclinical inflammation in the knee [26].

A recent study that analyzed MRI images of small joints (extremities) of patients who were ACPA-positive with arthralgia found that the degree of synovitis, bone marrow edema, and erosions were higher in the patients with arthralgia compared to healthy persons, but lower than that of ACPA-positive patients with RA (Figures 2.3 to 2.5). As such, these data are in line with those of a study on monkeys showing that subclinical inflammation precedes clinical arthritis [27]. This study also showed that, in monkeys, the preclinical phase was characterized by synovial tissue infiltration of macrophages and the expression of macrophage-derived cytokines.

Unclassified arthritis

Knowledge about the processes taking place during the aforementioned preclinical phases is at present relatively limited. Much more data are available on the phase of unclassified (also called undifferentiated) arthritis (UA); the vast majority of these studies were performed when RA was defined according to the 1987 American College of Rheumatology (ACR) criteria.

Clinical and serological risk factors for progression to RA are summarized in Table 2.4 and relate to the extent of inflammation and the presence of auto-antibodies.

With regards to imaging, positive findings have been found using ultrasound, digital X-ray radiogrammetry (DXR), and MRI (Table 2.5). Ultrasound has a predictive value for RA development that is independent of and additive to known serological and clinical risk factors for RA [28]. Measuring bone mass density via DXR also seems to be relevant, though the present studies on UA are based on rather low patient numbers [29]. Two studies were done on the value of extremity MRI in early UA; in both studies, bone marrow edema was most predictive for progression to RA (Table 2.5) [28–31]. In regards to MRI, it should be noted that it is not completely clear which abnormalities are diagnostic or prognostic, as erosions and synovitis have also been observed in healthy persons, to some extent (mostly RA MRI scoring grade 1). When using MRI, the present data indicate that bone marrow edema is most strongly associated with the development of RA (Figures 2.6 to 2.8) and progression of RA (Table 2.6) [32–35].

With the development of the 2010 ACR/EULAR criteria for RA, not only did the definition of RA change, but also the definition of UA. Some patients who were formerly classified as UA at first presentation are now identified as having RA when using the 2010 criteria; this predominantly concerns ACPA-positive patients with early arthritis. However, the opposite also occurs. A proportion of patients who at disease-onset fulfilled the 1987 criteria do not fulfill the 2010 criteria; these are generally ACPA-negative patients. Overall, patients with UA according to the 2010 criteria have milder baseline characteristics and outcomes than patients with UA according to 1987 criteria (Figure 2.9) [31]. Importantly, although the majority of patients with UA using 2010 criteria are ACPA-negative, up to 25% of these patients progress to RA after 1 year. At present, we do not have adequate predictive tools to identify these patients. Whether imaging modalities are helpful in patients with UA is presently under investigation.

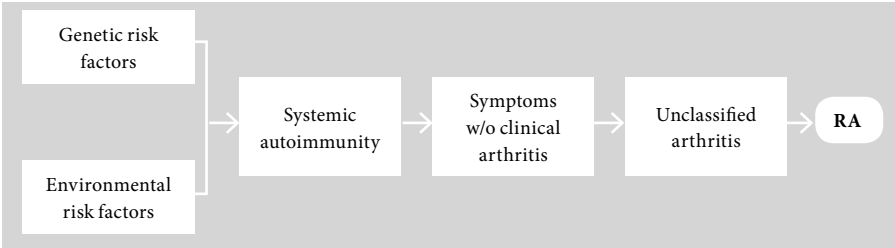


Figure 2.1 Different phases in the development of rheumatoid arthritis. RA, rheumatoid arthritis.

Genetic variant	Located in/nearby gene(s)	Locus	Minor allele frequency	OR (95%CI)
HLA-DRB1 shared epitope alleles		6p21	0.22	2.88 (2.73–3.03)
rs2476601	<i>PTPN22</i>	1p13	0.10	1.94 (1.81–2.08)
rs3087243	<i>CTLA4</i>	2q33	0.44	0.87 (0.83–0.91)
rs10499194	<i>TNFAIP3-OLIG3</i>	6q23	0.27	0.91 (0.87–0.96)
rs7574865	<i>STAT4</i>	2q32	0.22	1.16 (1.10–1.23)
rs10818488	<i>C5-TRAF1</i>	9q33	0.40	1.45 (1.12–1.88)
rs2104286	<i>IL-2RA</i>	10p15	0.24	0.93 (0.87–0.97)
rs743777	<i>IL-2RB</i>	22q12	0.33	1.11 (1.05–1.17)
rs6822844	<i>IL-21</i>	4q27	0.18	0.90 (0.84–0.95)
rs4810485	<i>CD40</i>	20q13	0.25	0.85 (0.80–0.90)
rs2812378	<i>CCL21</i>	9p13	0.34	1.10 (1.05–1.16)
rs3890745	<i>MMEL</i>	1p36	0.33	0.90 (0.86–0.94)
rs4750316	<i>PRKCQ</i>	10p15	0.19	0.87 (0.82–0.92)
rs1678542	<i>KIF5A</i>	12q13	0.38	0.91 (0.87–0.96)
rs42041	<i>CDK6</i>	7q21	0.24	1.08 (NP)
rs13031237	<i>REL</i>	2p16	0.37	1.13 (1.07–1.18)
rs2736340	<i>BLK</i>	8p23	0.25	1.12 (1.07–1.18)
rs394581	<i>TAGAP</i>	6q25	0.30	0.91 (0.87–0.96)
rs1980422	<i>CD28</i>	2q33	0.24	1.12 (1.07–1.17)
rs540386	<i>TRAF6</i>	11p12	0.14	0.88 (0.83–0.94)
rs10919563	<i>PTPRC</i>	1q31	0.13	0.88 (0.82–0.94)
rs12746613	<i>FCGR2A</i>	1q23	0.12	1.13 (1.06–1.21)
rs548234	<i>PRDM1</i>	6q21	0.33	1.10 (1.05–1.16)
rs11586238	<i>CD2/CD58</i>	1p13	0.24	1.13 (1.07–1.19)
rs10865035	<i>AFF3</i>	2q11	0.47	1.12 (1.07–1.17)
rs6859219	<i>ANKRD55/IL-6ST</i>	5q11	0.21	0.85 (0.78–0.93)
rs26232	<i>C5-orf30</i>	5q21	0.32	0.93 (0.88–0.98)
rs3093023	<i>CCR6</i>	6q27	0.43	1.11 (1.06–1.16)
rs10488631	<i>IRF5</i>	7q32	0.11	1.25 (1.14–1.37)
rs13315591	<i>PXK</i>	3p14	0.10	1.13 (1.04–1.23)
rs874040	<i>RBJP</i>	4p15	0.30	1.18 (1.12–1.24)
rs934734	<i>SPRED2</i>	2p14	0.49	1.13 (1.06–1.21)
rs951005	<i>CCL21</i>	9p13	0.16	0.87 (0.81–0.93)

Table 2.1 The first genetic risk factors that were replicated in independent studies and their odds on rheumatoid arthritis. CI, confidence interval; NP, not provided; OR, odds ratio.

Risk factor	Degree of evidence
Environment - Air pollution - Infections	Inconclusive - Increased RA risk has been reported [7] Inconclusive - Indirect evidence by findings of increased rates of onset of RA in the winter [4,8] - Several microorganisms have shown increased titres of antibodies in RA compared to controls, however no single microorganism seems responsible for RA-development [9,10]
Lifestyle factors - Smoking - Coffee - Alcohol	Established - This is the only well established environmental factor for RA [6] - Predisposition in HLA-DRB1 shared epitope-positive persons for development of ACPA-positive RA [11] Inconclusive - Both positive and negative effects have been observed Inconclusive - RA patients report lower intake of alcohol, unclear whether alcohol is truly protective [12]
Hormonal - Parity - Hormone replacement therapy/oral contraceptives - Breast feeding	Inconclusive - Some studies reported a lower RA risk in parous women [13,14] Inconclusive - Some studies reported on a decreased risk of RA [14,15] Inconclusive - A reduced risk for RA has been observed in women after long-term breast feeding [14,16]

Table 2.2 Environmental risk factors for rheumatoid arthritis. ACPA, anti-citrullinated peptide antibody; RA, rheumatoid arthritis.

Category	Serologic abnormality
Inflammation	- Increased CRP - TNF-α levels, several interleukins (ILs) (eg, IL-1α, IL-1β, IL-6, IL-10, IL-15) are increased
Auto-antibodies	- Increased prevalence of rheumatoid factor - Increased prevalence of ACPA positivity - Maturation of ACPA response
Metabolism	- Lower HDLc levels, lower ApoA levels - Increased P1NP and osteoprotegerin levels

Table 2.3 Reported serological abnormalities in the preclinical phase of (rheumatoid) arthritis. ACPA, anti-citrullinated peptide antibody; ApoA, apolipoprotein; CRP, C-reactive protein; HDLc, high density lipoprotein cholesterol; P1NP, serum procollagen type 1 amino-terminal propeptide; TNF- α , tumor necrosis factor-alpha.

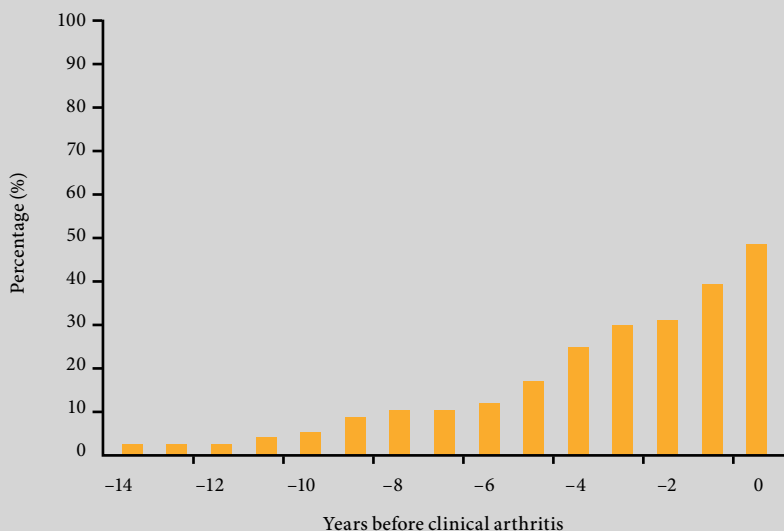


Figure 2.2 Percentage of patients with rheumatoid arthritis and positive for rheumatoid factor or anti-citrullinated peptide antibodies in the years before the onset of clinically detectable arthritis. Adapted with permission from Nielen et al [19] ©SAGE.

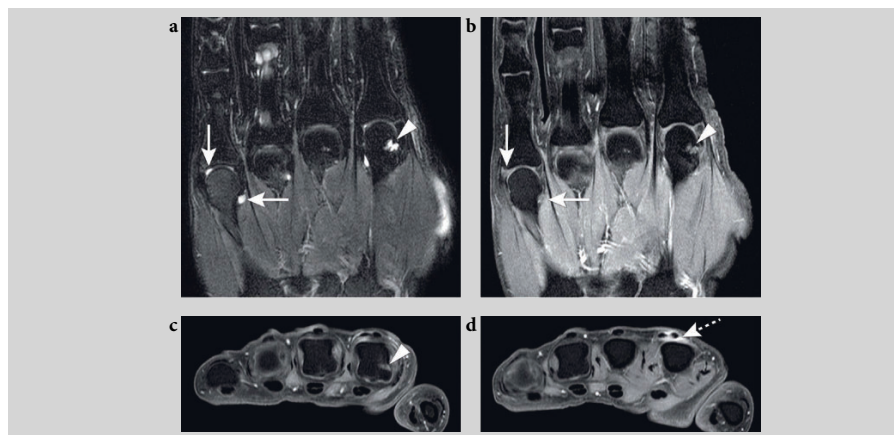


Figure 2.3 Magnetic resonance images of the left hand in a patient who is positive for anti-citrullinated peptide antibodies with arthralgia but without clinically-detectable arthritis. 1.5T extremity MRI with maximum field of view of 16 cm. Shown are the metacarpal bones 1 to 4 and the proximal phalanges. (a) Coronal T2 TSE fat saturation (fatsat) and (b, c, d) coronal and axial T1 TSE fatsat after intravenous administration of gadolinium. Some fluid is present in the fifth metacarpal phalangeal joint (a; arrows); the lack of enhancement after gadolinium shows there is no synovitis. In the head of metacarpal 2, subchondral cysts are appreciated (a), no enhancement is seen (b, c; arrow heads). However, on the axial images, the enhancement around the extensor tendons of the second finger is consistent with tenosynovitis (d; dotted arrow). In addition on the coronal T2 TSE, partial voluming of fluid, nonenhancing after gadolinium in the soft tissues dorsal to the fourth proximal phalanx is seen.

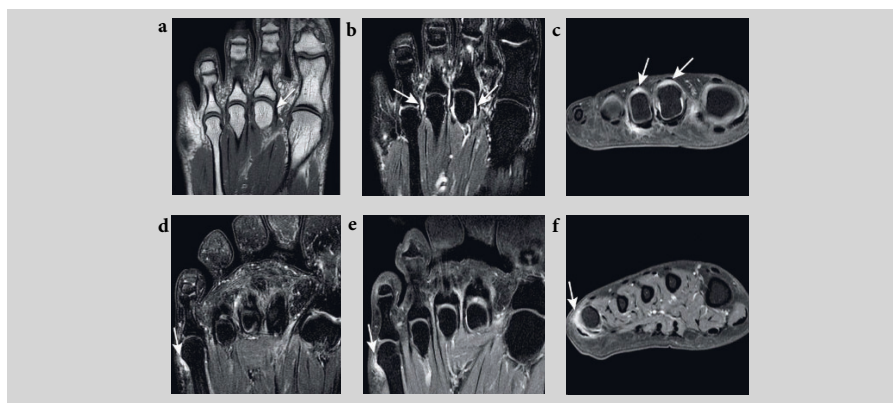


Figure 2.4 Magnetic resonance images (MRIs) of the left foot in a patient who is positive for anti-citrullinated peptide antibodies with arthralgia but without clinically-detectable arthritis. Axial T1 TSE (a), T2 TSE fat saturation (b, d), and axial and coronal T1 TSE fatsat with gadolinium (c, e, f) of the forefoot on 1.5T extremity MRI. Intact cortical bone of the metatarsal phalangeal (MTP) joints on T1 TSE image (a). The high signal intensity on T2 TSE in the MTP joints (b), enhances after gadolinium (c) and is consistent with synovitis. This is well visualized on the coronal T1 TSE fatsat images with gadolinium at the level of the MTP 2 and 3 (c; arrows). The MTP 5 joint shows high signal intensity on (d) axial T2, and enhancement on (e) axial and (f) coronal T1 TSE fatsat (arrows), also consistent with synovitis.

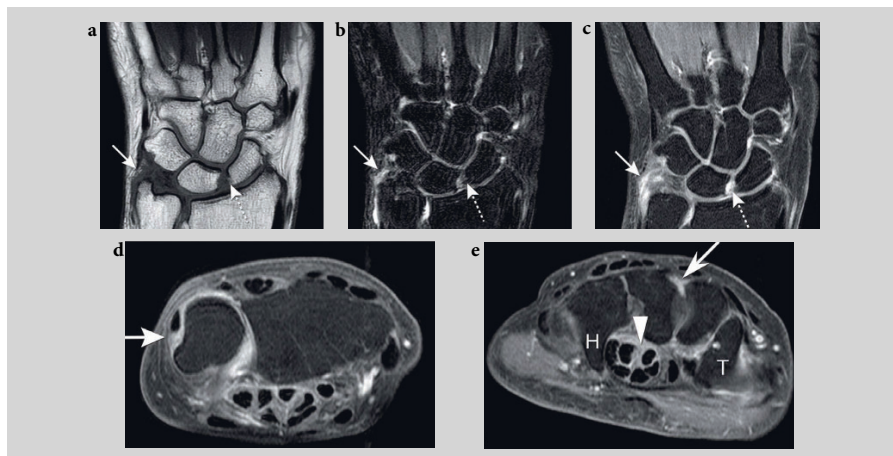


Figure 2.5 Magnetic resonance images (MRIs) of the left wrist with synovitis in a patient who is positive for anti-citrullinated peptide antibodies with arthralgia but without clinically-detectable arthritis. Coronal T1 TSE (a), T2-TSE fatsat (b) and T1 TSE fatsat with gadolinium, coronal (c), and axial (d) at the level of the distal radial ulnar joint and the carpal tunnel (e). The T2 images show some movement artefacts. Synovial thickening surrounding the distal ulna with irregularity of the triangular fibrocartilage, the signal intensity is intermediate on T1, inhomogeneous increased on T2, showing enhancement after intravenous gadolinium (d, e; arrow). Appreciate the cortical irregularity of the scaphoid and lunate (a, b) with enhancing synovium (c; dotted arrows). The radial styloid shows cortical irregularity as well (a, c). The axial image at the level of the distal carpal tunnel (H, hook of hamate; T, trapezoid) shows enhancement around the flexor tendons (arrow head) and between the capitatum and trapezium, consistent with (teno)synovitis (e; arrow).

Risk factors:

- Older age
- Female gender
- Positive family history for rheumatoid arthritis
- Gradual symptom onset
- Involvement of small joints
- Symmetric symptoms and signs
- High (4 or more) number of tender joints
- High (4 or more) number of swollen joints
- Morning stiffness
- Increased CRP
- Increased ESR
- Presence of rheumatoid factor
- Presence of ACPA
- Smoking

Table 2.4 Clinical and serological risk factors for development of rheumatoid arthritis in patients with unclassified arthritis. ACPA, anti-citrullinated peptide antibodies; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

	Characteristics predictive for RA development	Additive prognostic value to clinical and serologic risk factors?
Ultrasound	Grayscale wrist and metacarpophalangeal joint involvement Power Doppler involvement of metatarsophalangeal joint	Yes, based on a study in 58 patients. The AUC significantly improved from 0.905–0.962 [28]
Magnetic resonance imaging (MRI)	Bone marrow edema in wrist or metatarsophalangeal joint	Yes, based on a study of 116 patients, after adjustments for other variables, bone marrow edema has an OR of 1.4 for RA development [30]. In a second study of 129 patients, bone marrow edema had an additive value to ACPA positivity (PPV increased from 92% to 100%) [31]
Digital X-ray radiogrammetry (DXR)	Highly elevated BMD loss is associated with a PPV of 85% on RA development (OR=6.1)	<i>Perhaps.</i> BMD has an independent effect of ACPA (OR=4.1, 95% CI 0.8, 21.2). Definitive conclusions cannot be drawn due to small numbers and a large CI [29]

Table 2.5 Prognostic value of different imaging modalities in unclassified arthritis. ACPA, anti-citrullinated peptide antibody; AUC, area under the curve; BMD, bone mineral density; CI, confidence interval; OR, odds ratio; PPV, positive predictive value; RA, rheumatoid arthritis.

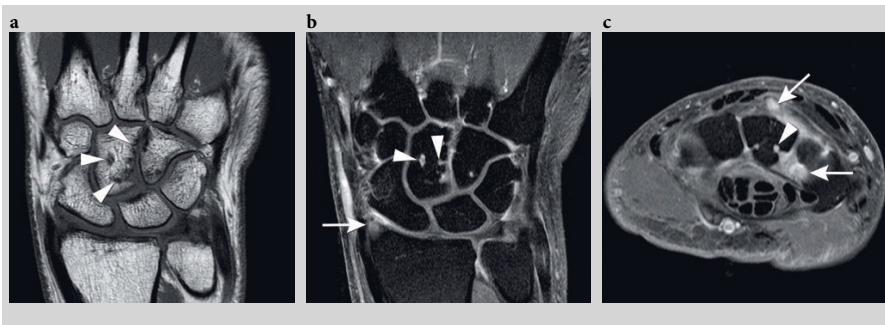


Figure 2.6 Magnetic resonance images (MRIs) of the right wrist in a patient with undifferentiated arthritis and erosions. Coronal T1 TSE (a), coronal (b) and axial (c) T1 TSE fat saturation (fatsat) with gadolinium. The multiple cortical defects are seen on coronal T1 TSE, enhancing on coronal and axial T1 TSE fatsat with gadolinium (arrow heads). Unsharply defined intraosseous enhancement is also present in the radial styloid (arrow), consistent with edema (b). Enhancing synovium is appreciated on the axial image intercarpal and at the dorsal side of the carpus (c; arrows).

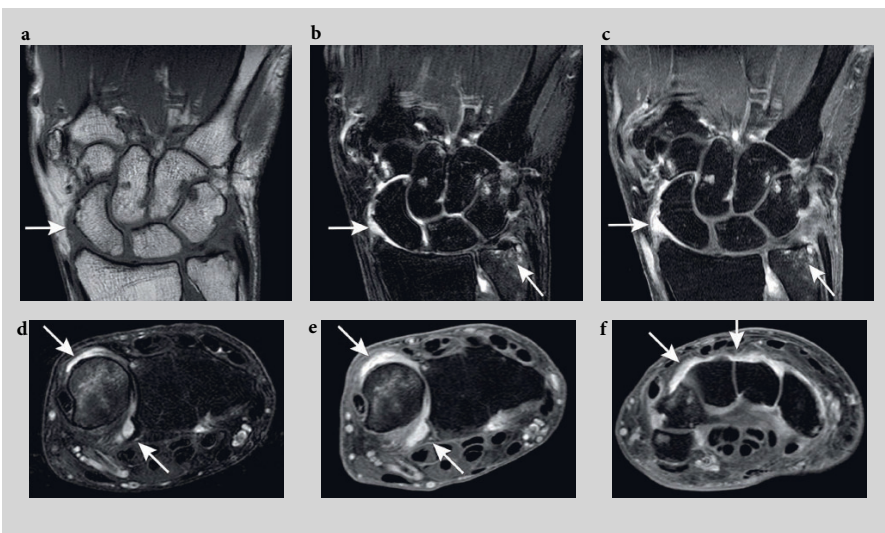


Figure 2.7 Magnetic resonance images (MRIs) of the right wrist in patient with undifferentiated arthritis and synovitis, intraosseous edema and erosions. Coronal T1 TSE (a), coronal and axial T2 TSE fat saturation (fat sat) (b,d) and coronal and axial T1 TSE fatsat with gadolinium (c, e, f). Multiple cortical erosions are visualized on T1 in the carpal bones and ulnar styloid process (a). On T2 (b) high signal intensity is present in the intercarpal, radiocarpal, and distal radial ulnar joints which enhances after contrast administration (c) (arrows), based on synovitis. Notice the intraosseous edema (bone marrow edema) and the enhancing erosions in the ulnar styloid (arrow). The high signal on T2 (d) is enhancing synovium (e) seen around the ulna and in the distal radial ulnar joint (arrows), as well as on the dorsal side of the carpalea (f).

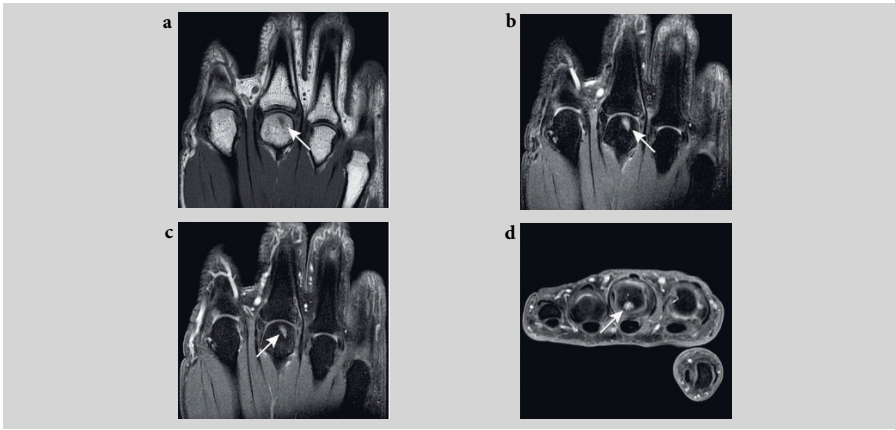


Figure 2.8 Magnetic resonance images (MRIs) of the right metacarpophalangeal joints in a patient with **unclassified arthritis**. Focal area in the head of metacarpal 3 of low signal intensity on T1 TSE (a), high on T2 TSE fat saturation (fatsat) (b), enhancing after gadolinium on T1 TSE fat sat (c, d). On the axial images, the volar subchondral location is appreciated, a cortical defect is not seen (however cannot be excluded). This finding is aspecific and can be based on a synovial cyst of no clinical importance or aspecific intraosseous edema. Its location, not at the level of ligamentous insertion, is less convincing for an erosion. There is no pathologic enhancing synovium. Follow-up in time may be of additional value.

Study [reference]	n	Disease duration (median)	Joints scanned	MRI scoring	Follow up	Outcome measure	Main finding
Haavardsholm et al [32]	84	<12 months	Wrist	RAMRIS	1 year	X-ray progression	BME independent predictor erosive progression
Syversen et al [33]	82	<12 months	Wrist	RAMRIS	1 year	X-ray progression	BME independent predictor erosive progression
Boyesen et al [34]	55	<12 months	Wrist	RAMRIS	3 years	X-ray progression	BME independent predictor erosive progression
Dohn et al [35]	52	7 years	Wrist, MCP	RAMRIS	1 year	X-ray progression	Especially BME predictive for erosive progression

Table 2.6 Overview of studies on magnetic resonance imaging in progression of rheumatoid and the main findings. BME, bone marrow edema; MCP, metacarpophalangeal joint; MRI, magnetic resonance imaging; RAMRIS, rheumatoid arthritis MRI score.

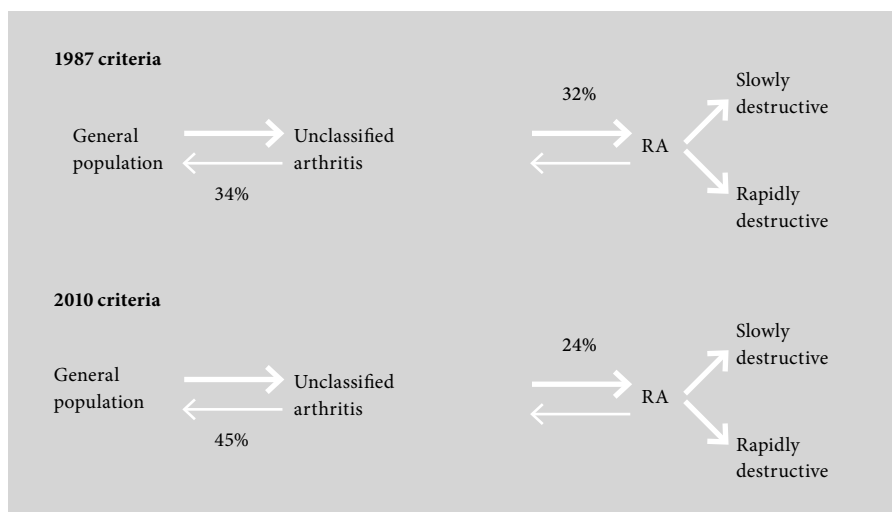


Figure 2.9 Outcomes of unclassified arthritis, depending on the classification method for rheumatoid arthritis. 1987 or 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria. RA, rheumatoid arthritis. Indicated are the percentages of patients with unclassified arthritis that achieved sustained remission after 7 years and the percentages of patients with unclassified arthritis that developed RA after 1 year [31].

References

- Gerlag DM, Raza K, van Baarsen LG, et al. EULAR recommendations for terminology and research in individuals at risk of rheumatoid arthritis: report from the Study Group for Risk Factors for Rheumatoid Arthritis. *Ann Rheum Dis*. 2012;71:638-641.
- van der Woude D, Houwing-Duistermaat JJ, Toes RE, et al. Quantitative heritability of anti-citrullinated protein antibody-positive and anti-citrullinated protein antibody-negative rheumatoid arthritis. *Arthritis Rheum*. 2009;60:916-923.
- Pedersen M, Jacobsen S, Klarlund M, et al. Environmental risk factors differ between rheumatoid arthritis with and without auto-antibodies against cyclic citrullinated peptides. *Arthritis Res Ther*. 2006;8:R133
- Symmons DP. Environmental factors and the outcome of rheumatoid arthritis. *Best Pract Res Clin Rheumatol*. 2003;17:717-727.
- Liao KP, Alfredsson L, Karlson EW. Environmental influences on risk for Rheumatoid Arthritis. *Curr Opin Rheumatol*. 2009;21:279-283.
- Linn-Rasker SP, van der Helm van Mil AH, et al. Smoking is a risk factor for anti-CCP antibodies only in rheumatoid arthritis patients who carry HLA-DRB1 shared epitope alleles. *Ann Rheum Dis*. 2007;65:366-371
- Hart JE, Laden F, Puett RC, Costenbader KH, Karlson EW. Exposure to traffic pollution and increased risk of rheumatoid arthritis. *Environ Health Perspect*. 2009;117:1065-1069.
- Schlesinger N, Schlesinger M. Seasonal variation of rheumatic diseases. *Discov Med*. 2005;5:64-69
- Loyola-Rodriguez JP, Martinez-Martinez RE, Abud-Mendoza C, Patiño-Marin N, Seymour GJ, et al. Rheumatoid arthritis and the role of oral bacteria. *J Oral Microbiol*. 2010;2.
- Söderlund M, van Essen R, Haapasaari J, Kiistala U, Kiviluoto O, Hedman K. Persistence of parvovirus B19 DNA in synovial membranes of young patient with and without chronic arthropathy. *Lancet*. 1997;349:1063-1065.

11. Klareskog L, Stolt P, Lundberg K, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. *Arthritis Rheum.* 2006;54:38-46.
12. Maxwell JR, Gowers IR, Moore DJ, Wilson AG. Alcohol consumption is inversely associated with risk and severity of rheumatoid arthritis. *Rheumatology (Oxford).* 2010;49:2140-2146.
13. Pikwer M, Bergström U, Nilsson JA, Jacobsson L, Berglund G, Turesson C. Breast feeding, but not use of oral contraceptives, is associated with a reduced risk of rheumatoid arthritis. *Ann Rheum Dis.* 2009;68:526-530.
14. Jorgensen C, Picot MC, Bologna C, Sany J. Oral contraception, parity, breast feeding, and severity of rheumatoid arthritis. *Ann Rheum Dis.* 1996;55:94-98.
15. Doran MF, Crowson CS, O'Fallon WM, Gabriel SE. The effect of oral contraceptives and estrogen replacement therapy on the risk of rheumatoid arthritis: a population based study. *J Rheumatol.* 2004;31:207-213.
16. Karlson EW, Mandl LA, Hankinson SE, Grodstein F. Do breast-feeding and other reproductive factors influence future risk of rheumatoid arthritis? Results from the Nurses' Health Study. *Arthritis Rheum.* 2004;50:3458-3467.
17. Rantapää-Dahlqvist S, de Jong BA, Berglin E, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. *Arthritis Rheum.* 2003;48:2741-2749.
18. Deane KD, O'Donnell CI, Hueber W, et al. The number of elevated cytokines and chemokines in preclinical seropositive rheumatoid arthritis predicts time to diagnosis in an age-dependent manner. *Arthritis Rheum.* 2010;62:3161-3172.
19. Nielsen MM, van Schaardenburg D, Reesink HW, et al. Simultaneous development of acute phase response and autoantibodies in preclinical rheumatoid arthritis. *Ann Rheum Dis.* 2006;65:535-537.
20. Karlson EW, Chibnik LB, Tworoger SS, et al. Biomarkers of inflammation and development of rheumatoid arthritis in women from two prospective cohort studies. *Arthritis Rheum.* 2009;60:641-652.
21. Turesson C, Bergström U, Jacobsson LT, et al. Increased cartilage turnover and circulating autoantibodies in different subsets before the clinical onset of rheumatoid arthritis. *Ann Rheum Dis.* 2011;70:520-522.
22. van Schaardenburg D, Nielsen MM, Lems WF, et al. Bone metabolism is altered in preclinical rheumatoid arthritis. *Ann Rheum Dis.* 2011;70:1173-1174.
23. van de Stadt LA, van Sijl AM, van Schaardenburg D, Nurmohamed MT. Dyslipidaemia in patients with seropositive arthralgia predicts the development of arthritis. *Ann Rheum Dis.* 2012; 71:1915-1916.
24. Bos WH, Wolbink GJ, Boers M, et al. Arthritis development in patients with arthralgia is strongly associated with anticitrullinated protein antibody status: a prospective cohort study. *Ann Rheum Dis.* 2010;69:490-494.
25. van de Stadt LA, Bos WH, Meursing Reynders M, et al. The value of ultrasonography in predicting arthritis in auto-antibody positive arthralgia patients: a prospective cohort study. *Arthritis Res Ther.* 2010;12:R98.
26. van de Sande MG, de Hair MJ, van der Leij C, et al. Different stages of rheumatoid arthritis: features of the synovium in the preclinical phase. *Ann Rheum Dis.* 2011;70:772-777.
27. Kraan MC, Versendaal H, Jonker M, et al. Asymptomatic synovitis precedes clinically manifest arthritis. *Arthritis Rheum.* 1998;41:1481-1488.
28. Filer A, de Pablo P, Allen G, et al. Utility of ultrasound joint counts in the prediction of rheumatoid arthritis in patients with very early synovitis. *Ann Rheum Dis.* 2011;70:500-507.
29. de Rooy DP, Kälvesten J, Huizinga TW, van der Helm-van Mil AH. Loss of metacarpal bone density predicts RA development in recent-onset arthritis. *Rheumatology (Oxford).* 2012;51:1037-1041.
30. Duer-Jensen A, Hørslev-Petersen K, Hetland ML, et al. Bone edema on magnetic resonance imaging is an independent predictor of rheumatoid arthritis development in patients with early undifferentiated arthritis. *Arthritis Rheum.* 2011;63:2192-2202.
31. Krabben A, Huizinga TW, van der Helm-van Mil AH. Undifferentiated arthritis characteristics and outcomes when applying the 2010 and 1987 criteria for rheumatoid arthritis. *Ann Rheum Dis.* 2012;71:238-241.
32. Haavardsholm EA, Bøyesen P, Østergaard M, Schildvold A, Kvien TK. Magnetic resonance imaging findings in 84 patients with early rheumatoid arthritis: bone marrow oedema predicts erosive progression. *Ann Rheum Dis.* 2008;67:794-800.

33. Syversen SW, Goll GL, Haavardsholm EA, Bøyesen P, Lea T, Kvien TK. A high serum level of eotaxin (CCL 11) is associated with less radiographic progression in early rheumatoid arthritis patients. *Arthritis Res Ther.* 2008;10:R28.
34. Bøyesen P, Haavardsholm EA, Ostergaard M, van der Heijde D, Sesseng S, Kvien TK. MRI in early rheumatoid arthritis: synovitis and bone marrow oedema are independent predictors of subsequent radiographic progression. *Ann Rheum Dis.* 2010;70:428-433.
35. Döhn UM, Ejbjerg B, Boonen A, et al. No overall progression and occasional repair of erosions despite persistent inflammation in adalimumab-treated rheumatoid arthritis patients: results from a longitudinal comparative MRI, ultrasonography, CT and radiography study. *Ann Rheum Dis.* 2010;70:252-258.

3 Early rheumatoid arthritis

Jackie L Nam

Introduction

Rheumatoid arthritis (RA) is the most common inflammatory arthritis, with an approximate prevalence of 1% worldwide [1–3]. It has a female:male ratio of about 3:1 and although age of onset is commonly over 50 years, it may occur at any age [2,4]. It is a systemic autoimmune disease with predominant joint involvement and typically presents with involvement of the small joints of the hands and feet. Untreated, the disease has been associated with increased morbidity and mortality, with cardiovascular involvement as one of the contributing causes [5–7]. A better understanding of the disease pathogenesis, early diagnosis and treatment, and the availability of targeted therapies have led to improved outcomes.

Whereas previously, early RA was defined by disease duration of a few years, the aim now is to see and treat RA as soon as possible. The concept of a ‘window of opportunity’ suggests that there is a period early in the course of the disease when the disease process can be altered or maybe even reversed with a complete return to normality. Therapy during this period may have a much greater effect than treatment at a later stage in terms of halting disease progression and achieving remission. This window for optimal outcomes is thought to be within weeks of symptom onset.

Seeing patients at the earliest opportunity requires early symptom recognition and referral to rheumatology services for assessment and decisions regarding therapy. Whilst the majority of patients with very early inflammatory arthritis will progress to RA, a proportion may undergo spontaneous

remission and others progress to other diseases (eg, systemic lupus erythematosus [SLE]). Use of laboratory tests including serological markers and newer imaging modalities such as magnetic resonance imaging (MRI) and ultrasound (US) are becoming more widely used to aid diagnosis. The 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) RA classification criteria have also been developed to replace the 1987 criteria, enabling classification of patients with RA at an earlier stage of the disease [8].

Therapy for RA includes both non-pharmacological and pharmacological measures. Patient education and input from health professionals (physiotherapy, occupational therapy, and podiatry) form an integral part of early RA management. Pharmacological treatment includes general therapies (eg, non-steroidal anti-inflammatory drugs [NSAIDs]) and specific disease-modifying antirheumatic drugs (DMARDs).

In terms of DMARD therapy, several important treatment principles have emerged. The first is that of early intervention with effective and appropriate treatment. Studies have demonstrated that early initiation of DMARD therapy is key to achieving good clinical outcomes and minimizing bone damage in patients with RA [9]. Of the synthetic DMARDs, methotrexate (MTX) remains the cornerstone of treatment [10]. In recent years, the emergence of more targeted biological DMARDs have further improved outcomes for patients with RA. Due to cost and availability, they are mainly reserved for patients who have failed treatment with synthetic DMARDs, although there is some evidence for their use in synthetic DMARD-naïve patients with the ability to achieve sustained responses, including biologic and drug-free remission in some [11–13]. Glucocorticoids also form part of the therapeutic armamentarium in RA for remission induction and are often used as bridging therapy and for management for disease flares [14].

The second principle is one of treating to target to achieve tight control of disease activity [15]. The use of strategies whereby patients are monitored regularly and treatment escalated if an outcome is not achieved is widely used in other areas of medicine, including the management of hypertension and diabetes mellitus. In practice, for patients with RA, this means that therapy is increased if disease activity is not suppressed below a predefined level (ideally remission or, in patients with long-standing disease, a state of low disease activity). This chapter will discuss the diagnosis and treatment of early RA in more detail.

Pathology in early rheumatoid arthritis

RA is a systemic autoimmune disease affecting mainly synovial lined joints. In early RA, the joint capsule, the outermost layer of the joint, remains unaffected. The synovial lining, which is usually two cell layers thick, becomes inflamed. The pannus that subsequently develops erodes cartilage and bone, resulting in joint destruction (Figure 3.1) [16].

Window of opportunity

The concept of a ‘window of opportunity’ underpins the rationale for the management of early RA, which aims to diagnosis and treat the disease at the earliest opportunity to achieve maximal benefit. As previously mentioned, it is based on the belief that there is a critical period during the early stages of the disease during which treatment is more effective than later on. This concept is supported by several studies. In an early arthritis cohort, assessment of patients with symptom onset <12 weeks was associated with a hazard ratio of 1.87 for achieving DMARD-free remission and a 1.3 times lower rate of joint destruction over 6 years, as compared with assessment at ≥12 weeks [17]. A meta-analysis examining the long-term impact on radiographic progression of early DMARD therapy showed that patients commencing therapy earlier (an average of 9 months) had a 33% reduction in long-term progression rates compared to those treated later (Figure 3.2) [18].

Diagnosis of early rheumatoid arthritis

In an attempt to diagnose and treat RA at the earliest opportunity, patients are being seen earlier in the course of their disease. A sizable proportion of patients who present with an inflammatory arthritis may have an undifferentiated arthritis (UA) – a form of arthritis that does not fulfill classification criteria for a more definitive diagnosis (Figure 3.3). The outcome of these patients varies and the diagnosis may change during the initial follow-up period. Whilst some will progress to RA, a proportion may develop other rheumatic diseases and others will remain undifferentiated or enter into spontaneous remission. Estimates from the Leiden Early Arthritis Clinic suggest that of the patients who present with UA, 30% will develop RA (based on the 1987 ACR classification criteria), up to 20% remain undifferentiated, and 30% will remit [19]. Clinicians, therefore, need to identify patients with inflammatory

arthritis and differentiate those with self-limiting disease from those with early RA, enabling the initiation of appropriate therapy for those who will progress and preventing unnecessary treatment for those with RA that will resolve. The following steps are suggested as an approach to the evaluation of patients with early arthritis [20]:

- recognize the presence of inflammatory arthritis;
- exclude diseases other than RA or UA that present as an early inflammatory arthritis (eg, SLE, psoriatic arthritis, or other spondyloarthropathy); and
- estimate the risk of developing persistent or erosive irreversible arthritis in patients with RA or UA by using a combination of clinical features, laboratory tests, and imaging techniques.

Clinical examination

A clinical examination and finding joint swelling not caused by trauma or bony swelling suggests a diagnosis of early RA, especially if it includes involvement of at least two joints and/or early morning stiffness lasting 30 minutes or more (Figure 3.4). Symmetric involvement of the hands is a hallmark of RA (Figure 3.5) [21]. Hand or foot involvement is common and in cases of early RA may be detected by a positive metacarpophalangeal (MCP) or metatarsophalangeal (MTP) squeeze test (Figure 3.6) [22].

Differential diagnosis of early rheumatoid arthritis

Clinical and laboratory features of diseases that may be considered in the differential diagnosis of early rheumatoid arthritis (Table 3.1) [23]. Articular symptoms may be the presenting manifestation of many infectious, inflammatory, or malignant conditions. A thorough history and clinical examination including symptom duration, early morning stiffness, the distribution of joint involvement, response to NSAIDs, any prodromal illness, and associated features will help differentiate between the conditions. Family history is also important for RA, psoriasis, and other autoimmune diseases. Laboratory investigations and imaging may be of additional benefit; however, it is important to be aware of the limitations when interpreting the results (eg, false positive and negative results.)

Serological markers in early rheumatoid arthritis

Rheumatoid factor (RF) is both a marker of persistence in patients with early inflammatory arthritis [24,25] and a predictor of radiographic progression [26,27]. Studies have shown sensitivities ranging from 41–66% and specificities between 87–97% (Table 3.2) [28].

Research into autoantibodies other than RF in sera of patients with RA led to the discovery of antibodies to citrulline, a non-standard amino acid that is generated by the post-translational modification of arginine residues by the enzyme peptidylarginine deiminase (PAD). The assay using the second-generation cyclic citrullinated peptide (CCP-2) as an artificial autoantigen is currently the most commonly used test in clinical practice to identify the antibodies to citrullinated peptides/proteins (ACPA). A review of data has shown that ACPA (or CCP-2) has a similar sensitivity to RF in early RA cohorts, but with a greater specificity. ACPA testing may be of particular value in detecting patients with RA who are RF-negative. ACPA positivity has also been shown to be an independent predictor of radiographic damage and progression [29].

Imaging in early rheumatoid arthritis

Conventional radiographs remain the most widely used imaging modality for detecting early RA given their low cost and availability. However, they are not very sensitive for detecting change in early RA. Newer imaging modalities (eg, MRI and US) have been shown to be more sensitive for visualizing early inflammatory and destructive change in RA and predicting future radiographic damage. However, relatively high costs, long examination times, and low availability limit the widespread use of MRI. US, in comparison, is relatively inexpensive, non-invasive, and allows many joints to be assessed at any one time. The main disadvantage of this modality is its dependency on the skills of the operator and potential problems with reproducibility. Table 3.3 shows a summary of some of the differences between the three imaging modalities and the advantages and disadvantages of each [23].

Conventional radiographs often appear normal in early RA. If radiographic erosions are present, they have a high specificity in discriminating between self-limiting and persistent inflammatory arthritis [30,31]. Baseline radiographic damage is also the best predictive factor of long-term structural outcome [32].

Radiographic examinations generally include the hands and feet. In approximately 14–18% of patients, cases are only detected in the feet (Figure 3.7) [33,34]. In general, anteroposterior views are done; other views (eg, lateral or oblique views) may be requested if clinically indicated. In cases where a diagnosis of early RA is suspected and conventional radiography is normal, MRI may be helpful to make a diagnosis (Figure 3.8). US is also a sensitive imaging modality for detecting soft tissue change in early RA (Figure 3.9).

Classification of rheumatoid arthritis

Recent work through a collaborative initiative between the ACR and EULAR to define RA at an early stage has enabled the development of new classification criteria for RA. The emphasis of the 2010 ACR/EULAR RA classification criteria is on identifying patients with a relatively short duration of symptoms who will benefit from early diagnosis and early institution of DMARD therapy (see Figure 1.1) [8].

Patients must meet two mandatory requirements for the classification criteria to be applied. First, there must be clinical evidence of synovitis (ie, swelling) in at least one joint. All joints of a full joint count may be assessed for this purpose with the exception of the distal interphalangeal (DIP) joints, the first MTP joint, and the first carpometacarpal (CMC) joint, as these joints are typically involved in osteoarthritis. Second, the synovitis should not be better explained by another diagnosis (eg, SLE, psoriatic arthritis, gout). Classification as definite RA is then based on achieving a total score of 6 or greater (out of 10) from individual scores in four domains. These are:

- number and site of involved joints (score range 0–5);
- serological abnormality (score range 0–3);
- elevated acute phase response (score range 0–1); and
- symptom duration (score range 0–1).

As a caveat, patients with RA-type erosions on X-ray with a typical history of RA may also be classified as such and the scoring system need not be applied.

Management of early rheumatoid arthritis

Synthetic disease-modifying antirheumatic drugs

Early treatment with DMARDS is one of the key principles in the treatment of early arthritis. Synthetic DMARDs have an effect on the disease process within weeks to months. MTX, sulphasalazine (SSZ), and leflunomide are commonly used DMARDs that have been shown to improve clinical outcomes and delay radiological progression. Of the synthetic DMARDs, MTX is considered the anchor drug and is generally used first in patients at risk of developing persistent disease or erosive disease because of its relatively beneficial safety profile, clinical and radiological efficacy, and its beneficial properties in treatment combinations with

biological DMARDs. Leflunomide and SSZ have similar clinical efficacy and are considered good alternatives (Figure 3.10) [35].

Biologic disease-modifying antirheumatic drugs

In recent years, biological therapies have become available for treating patients with early RA. Tumor necrosis factor alpha (TNF- α) is one of the cytokines that is central to the inflammatory cascade. It has pleiotropic effects driving the immune response, with modulatory effects on many aspects of cellular and humoral immunity, and has an important role in persistence of early RA. Other biological DMARDs with different modes of action have also come to the fore. For example, the biological DMARDs used in the treatment of RA include infliximab, adalimumab, etanercept, as well as golimumab and certolizumab, two newer TNF inhibitors; rituximab, a B-cell-depleting agent; abatacept, an inhibitor of T cell co-stimulatory pathways; and tocilizumab, an interleukin (IL)-6 receptor antagonist [36]. These agents provide rapid control of inflammation and have proven efficacy both in terms of clinical outcomes and structural damage [37]. They are, however, substantially more expensive than traditional DMARDs and are generally used in patients who have failed therapy with synthetic DMARDs [38]. Selecting patients with poor prognostic factors for early biologic DMARD therapy may improve this cost-benefit balance.

In the Combination Of Methotrexate and ETanercept (COMET) study [39], the first major study looking at remission as the primary endpoint in patients with early RA, patients with symptom duration of 2 years or less were randomized to receive MTX or MTX plus the TNF inhibitor etanercept for a year (52 weeks). At week 52, remission as defined by a disease activity score in 28 joints (DAS28) of <2.6 was achieved in 49.8% of patients given MTX plus etanercept, versus 27.8% with MTX alone ($P<0.001$) (Figure 3.11) [39]. Radiographic progression at week 52 was also significantly lower in the group receiving combination therapy.

Induction with biological and maintenance with synthetic disease-modifying antirheumatic drugs

Induction with biological and maintenance with conventional DMARDs is a therapeutic strategy in patients with early RA introduced in a placebo-controlled study by Quinn et al [11]. The study demonstrated that patients with early RA and poor prognostic factors treated

with infliximab and MTX developed less MRI-detected erosions at 12 months than patients treated with MTX alone (Figure 3.12) [11].

Monitoring of disease activity and achieving tight control

The primary goal of treating the patient with RA is to maximize long-term health-related quality of life through control of symptoms, prevention of structural damage, normalization of function, and social participation [39,40]. To achieve this, the optimal initial treatment may be less a matter of drug choice and more of a question of whether treatment is adjusted to minimize the burden of disease.

In the Tight Control in Rheumatoid Arthritis (TICORA) study, 110 patients with RA of less than 5 years' duration were randomly assigned to an intensive treatment in order to reach a low activity state (disease activity score in 44 joints [DAS44]<2.4) close to remission or to regular clinical care (Figure 3.13) [41,42]. Patients in the TICORA group were examined monthly and DMARD therapy was escalated according to a predefined strategy if the DAS44 was >2.4. Those in the routine care group were seen every 3 months without formal assessment or feedback on disease activity scores and therapy adjusted according to the clinical judgment of the rheumatologist. The intensive treatment group had significantly more patients in remission and developed less radiographic damage than the control group after 18 months of follow-up. This strategy also resulted in a higher treatment retention rate, a lower rate of discontinuations due to side effects, and lower costs per patient (based on lower admission costs) than routine care over the 18 months of observation. Of note, more intra-articular steroids were used in this treatment group. Other clinical trials have confirmed the benefits of this treat to target approach [42].

Treating to target

Regular monitoring and treatment aiming at specific therapeutic targets has led to improved outcomes and a reduction in the risk of organ damage in several areas of medicine (eg, the treatment of diabetes and hypertension). Based on evidence from the systematic literature

review and expert opinion on best practice [43], recommendations for achieving optimal therapeutic outcomes for RA were developed by a task force of rheumatologists and a patient.

In Figure 3.14, the main target (remission and sustained remission) and the alternative target (low disease activity in patients with long-term disease) are indicated as separate threads [41]. Remission, defined as the absence of signs and symptoms of significant inflammatory disease activity, is the primary target for treatment of RA. In certain instances (eg, in established long-standing disease), low disease activity may be an acceptable alternative therapeutic goal. The approaches to attain the targets and sustain them are similar.

Assessments should be performed with appropriate frequency and using composite disease activity measures which include joint counts. Structural damage should be assessed with X-rays approximately every 12 months during the first few years. Functional assessment (for example, the Health Assessment Questionnaire disability index) may be used to complement the disease activity and structural damage monitoring [44].

Measures of disease activity

Monitoring of disease activity should include tender and swollen joint count, patient and physician global assessment, ESR, and CRP. Composite scores have been developed using a combination of these variables (Tables 3.4 and 3.5) [45,46]. The choice of the composite measure of disease activity and the level of the target value may be influenced by consideration of comorbidities, patient factors, and drug-related risks.

Clinical trials using different treatment combinations together with treat to target strategies in early rheumatoid arthritis

Several studies in DMARD-naïve early RA have incorporated treat to target type approaches within their treatment strategies (Table 3.6) [12,47–55]. These have shown good clinical outcomes in all patients irrespective of the initial treatment groups reinforcing the importance of early intervention and tight control in the treatment of RA [55]. Overall, the more intensive strategies have shown the added benefit of earlier clinical responses [12,50,54], lower long-term

radiographic progression, and the potential for drug-free remission [47,56]. Several other trials in MTX-naïve RA support these findings [57–59].

Recommendations for the management of early rheumatoid arthritis

The following are a summary of points to consider in the management of patient with early RA (Table 3.7) [59,60]:

- early diagnosis and treatment can prevent or delay the joint destruction, functional impairment, and mortality associated with rheumatoid arthritis;
- early recognition of an inflammatory arthritis is therefore imperative;
- patients with an inflammatory arthritis should be referred as early as possible to a rheumatologist for further management;
- a combination of clinical, imaging, and laboratory measures will allow the clinician to differentiate between causes of an inflammatory arthritis from rheumatoid arthritis;
- early effective therapy should be instituted for those at risk of developing a persistent and/or erosive arthritis;
- therapy includes both pharmacological and non-pharmacological measures; and
- the best treatment is a combination of optimal drug therapy, regular monitoring, and intervention to achieve remission or low disease activity.

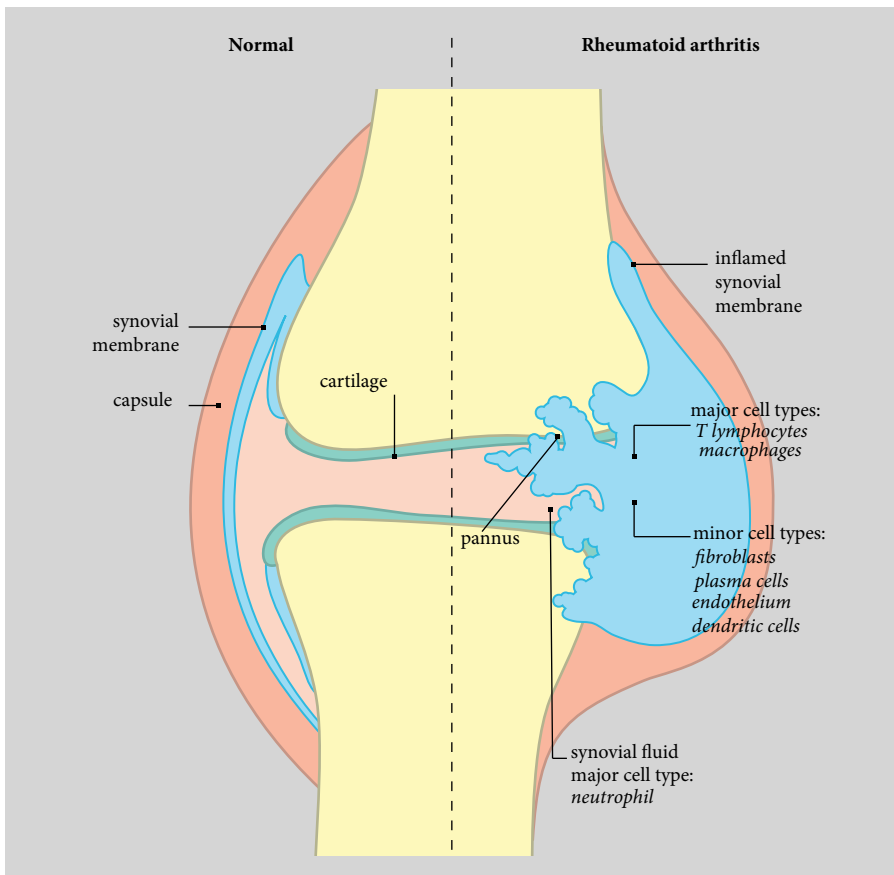


Figure 3.1 Synovial joint in health and rheumatoid arthritis indicating cellular components and sites of destruction in diseased joint. Reproduced with permission from Taylor [16] ©Humana Press.

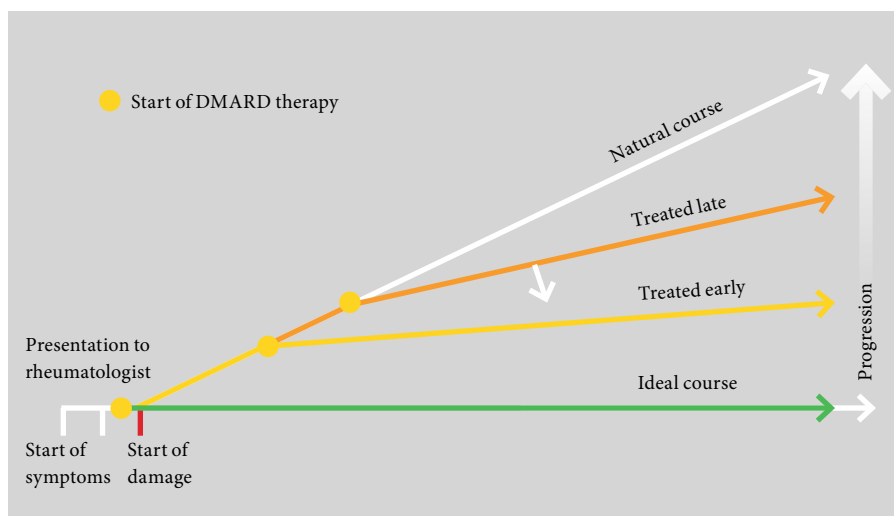


Figure 3.2 Altering the course of early rheumatoid arthritis. Untreated, most patients with rheumatoid arthritis (RA) will follow a course of progressive joint damage, increased morbidity, and mortality. Earlier treatment, however, has shown to alter this course. Ideally patients should be diagnosed at the earliest stages and disease-modifying antirheumatic drugs (DMARDs) commenced. Reproduced with permission from Breedveld and Kalden [18]©Sage.

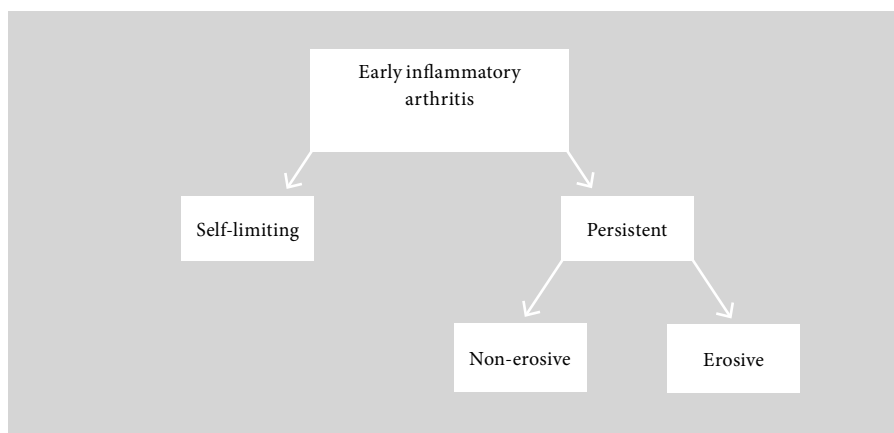


Figure 3.3 Natural history of inflammatory arthritis. A sizable proportion of patients who present with an inflammatory arthritis may have an undifferentiated arthritis, a form of arthritis that does not fulfill classification criteria for a more definitive diagnosis. The outcome of these patients varies and the diagnosis may change during the initial follow-up period. Whilst some will be persistent and may develop erosive disease, others may be self-limiting and enter into spontaneous remission.



Figure 3.4 Clinical examination of the hand. The clinical examination remains the cornerstone for evaluating patients to determine whether arthritis is present or not, differentiate between inflammatory or non-inflammatory disease, and decide the etiology of the arthropathy.



Figure 3.5 Clinical features of the hand in early rheumatoid arthritis. There may be swelling of the wrists, metacarpophalangeal joints, or the proximal interphalangeal joints. There is no deformity. There is bilateral involvement of the wrists and metacarpophalangeal joints of this 54-year-old woman, who had had synovitis for about 10 weeks at the time this photograph was taken. Reproduced with permission from Matteson et al [21] ©Springer.

Arthritis type	Personal history	Typical pattern of joint involvement
Undifferentiated arthritis (nonprogressive)	F>M	Insidious Oligoarthritis
Rheumatoid arthritis	F>M; 35–50 years	Insidious progressive symmetrical
Spondyloarthropathy	Psoriasis Urethritis or cervicitis IBD Family history of psoriasis or IBD	Persistent asymmetric oligoarticular
Systemic lupus erythematosus	F>M Young	Polyarticular, symmetric, usually nonerosive
Viral (HBV, HCV)	Hepatitis risk factors	Acute polyarthritis
Septic arthritis (nongonococcal)	Peak incidence in elderly Reduced host immunity Joint prostheses	Acute Monoarticular Often extremely painful (may be polyarticular)
Gonococcal	F>M Young Sexually active	Acute oligo- or polyarthritis
Osteoarthritis	F>M, Men with knee or hip involvement ↑Age	Progressive oligo- or polyarticular asymmetric or symmetric, bony swelling
Gout	Men Postmenopausal women, Diuretic use (especially in elderly)	Sudden onset Severe pain with attacks Oligoarticular early Polyarticular later
Pseudogout	M=F ↑Age	Chronic Oligo- or polyarticular Acute monoarticular (25%)

Table 3.1 Clinical and laboratory features of diseases that may be considered in the differential diagnosis of early rheumatoid arthritis (*continued overleaf*)

Joints affected	Associated features	Laboratory tests
PIP, MCP, wrist, MTP, knee, ankle	-	↑CRP/ESR
PIP, MCP, wrist, MTP, knee, ankle	EMS	↑CRP/ESR RF+ CCP+
DIP, PIP, knee, feet, spine	Psoriasis Nail pitting Uveitis Enthesitis Dactylitis	ESR/CRP may be normal More severe course in HLA B27 +
PIP, knee	Rash Serositis	Anemia ↑ESR/CRP Proteinuria ANA+ dsDNA+
PIP, MCP, wrist, knee, ankles	Jaundice	↑ESR/CRP ↑ LFTs Hepatitis B and C serology
Knee (most common), hip, shoulder, ankle, wrist	Systemic symptoms common	<i>Staphylococcus aureus</i> (most common) Synovial fluid is gram-stain positive in 50% and culture positive in 90%
Wrist, knee	Fever Rash Skin blisters/pustules, Tenosynovitis	↑ESR/CRP ↑WBC Synovial fluid gram-stain positive in 25% and culture positive in 50% of cases
DIP, PIP, First CMC1, knee, hip, MTP, spine	-	Normal laboratory tests
MTP, toes, ankle, knees	Tophi	Synovial fluid Urate crystals ↑Uric acid level (normal levels in 40% of acute attacks)
Knee, wrist, finger, MTP	Hypomagnesemia Hypophosphatemia Hemochromatosis Wilson's disease Hyperparathyroidism	↑CRP ↑WBC

Arthritis type	Personal history	Typical pattern of joint involvement	Joints affected	Associated features	Laboratory tests
Polymyalgia rheumatica	M=F Older Caucasian	Prolonged morning stiffness	Hip and shoulder girdle, PIP wrist knee occasionally	RS3PE	Anemia ↑ESR/CRP
Sarcoidosis	F>M	Acute symmetrical Chronic uncommon	Knees ankles	Fever Erythema nodosum Hilar lymphadenopathy with acute sarcoid	↑ESR/CRP Serum ACE
Scleroderma	F>M	Acute or occasionally, insidious symmetric or asymmetric	MCP, PIP Tendon friction rubs (diffuse disease)		↑CRP/ESR ANA + Scl-70+ ACA +

Table 3.1 Clinical and laboratory features of diseases that may be considered in the differential diagnosis of early rheumatoid arthritis (*continued*). ACA, antinuclear antibody; ANA, antinuclear antibody; CCP, cyclic citrullinated peptide; CMC1, first carpometacarpal joint; CRP, C-reactive protein; EMS, early morning stiffness; ESR, erythrocyte sedimentation rate; F, female; HBV, hepatitis B virus; HCV, hepatitis C virus; IBD, inflammatory bowel disease; LFT, liver function test; M, male; MCP, metacarpophalangeal joint; MTP, metatarsophalangeal joint; PIP, proximal interphalangeal joint; RF, rheumatoid factor; WBC, white blood cells. Reproduced with permission from Nam et al [23] ©BMJ.

	ACPA (CCP-2)	IgM-RF	ACPA (CCP-2) or IgM-RF	ACPA (CCP-2) and IgM-RF
Sensitivity range (%)	41–63	41–66	52–67	33–58
Specificity range (%)	91–100	81–97	72–82	98–100

Table 3.2 Performance of immunoglobulin M-rheumatoid factor and anti-citrullinated peptide antibodies (cyclic citrullinated peptide 2) assays in early rheumatoid arthritis cohorts. ACPA, anti-citrullinated peptide antibody; CCP-2, cyclic citrullinated peptide 2; IgM-RF, IgM rheumatoid factor. Adapted with permission from Aggarwal et al [28] ©Wiley.

	Conventional radiography	MRI	Ultrasound
Tolerance	Excellent	Fair	Excellent
Ionizing radiation	Yes	No	No
Time to perform	Short	Long	Intermediate
Cost	Inexpensive	Expensive	Inexpensive
Ease of accessibility	Easy	Intermediate/difficult*	Easy-difficult*
Operator dependant	No	No	Yes
Number of joints per session	Many	Few	Many
Planes	One	Multi	Multi
Real-time scanning	No	No	Yes
Bone visualization	Good	Excellent	Good (cortex only)
Soft tissue visualization	Non-specific	Excellent	Excellent
Allows intervention	Yes (fluoroscopy)	No	Yes

Table 3.3 Imaging modalities in used in early rheumatoid arthritis. MRI, magnetic resonance imaging. *dependent on availability. Adapted with permission from Nam et al [23] ©Humana Press.

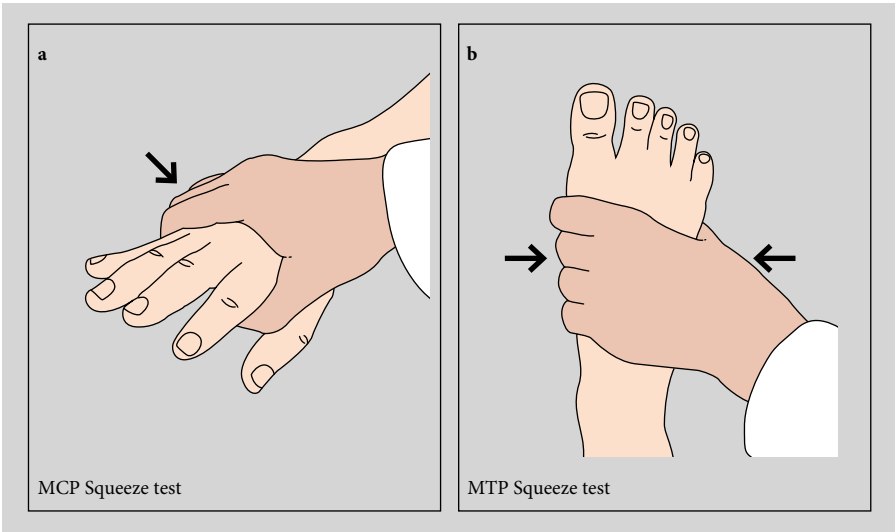


Figure 3.6 Metacarpophalangeal and metatarsophalangeal squeeze test. Hand or foot involvement is common and in cases of early RA and may be detected by a positive metacarpophalangeal (MCP) or metatarsophalangeal (MTP) squeeze test. This involves squeezing the patient's hand (a) or foot (b) across the knuckle joints. Adapted with permission from Arthritis Research UK [22] ©Arthritis Research UK.



Figure 3.7 Conventional radiograph of the foot showing erosion of the fifth metatarsal head. Reproduced with permission from European League Against Rheumatism [33] ©EULAR.

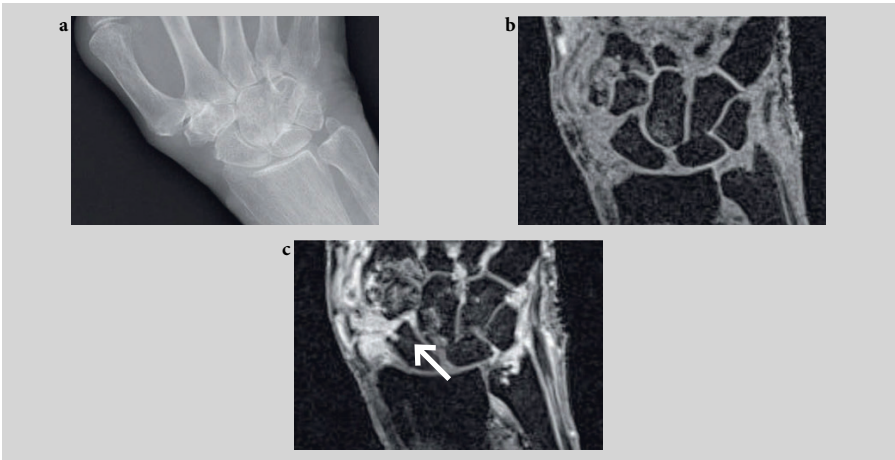


Figure 3.8 Magnetic resonance imaging in early rheumatoid arthritis. In this patient with early rheumatoid arthritis (RA), although the scaphoid erosion is not seen on the conventional radiograph of the (a) wrist and hand or (b) the precontrast MRI image, it is visualized on the (c) post-contrast MRI image. Synovitis and bone marrow edema are other findings on MRI and indications of soft tissue involvement in early RA. Reproduced with permission from University of Leeds, UK.

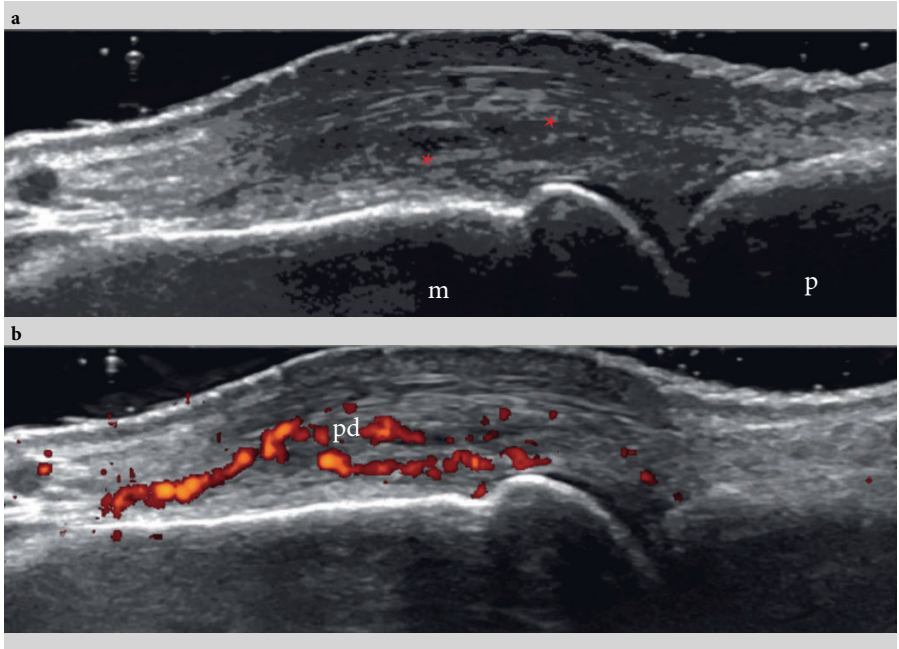


Figure 3.9 Ultrasound in early rheumatoid arthritis. In this longitudinal dorsal ultrasound scan of a metacarpophalangeal joint of a patient with early rheumatoid arthritis (RA), the grayscale (a) change and power Doppler signal (b) suggest inflammatory arthritis disease activity. *synovial hypertrophy. m, metacarpal head; p, proximal phalanx; pd, power Doppler. Reproduced with permission from University of Leeds, UK.

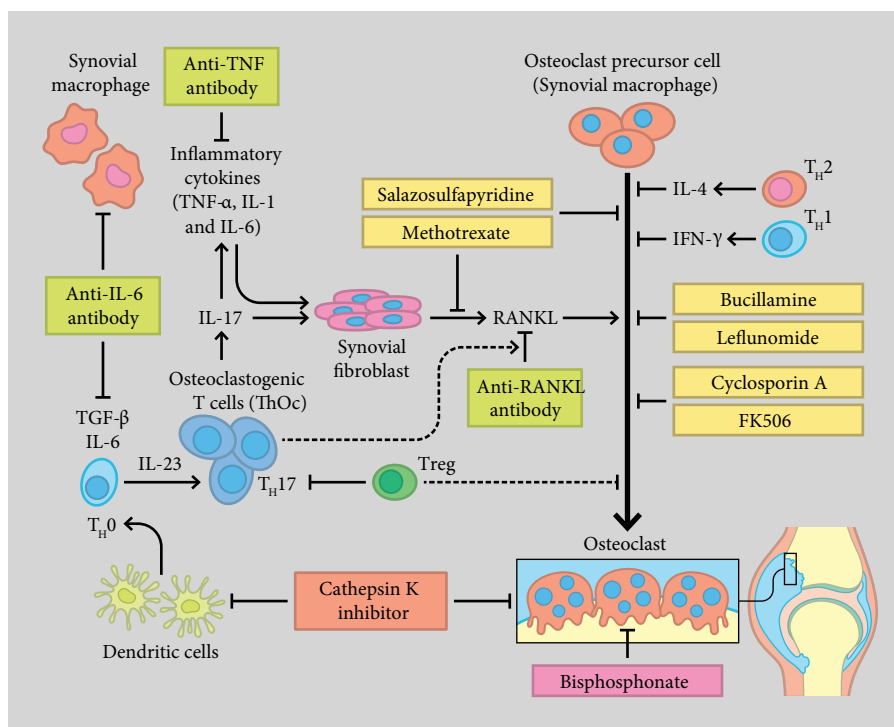


Figure 3.10 Methotrexate, sulphasalazine and leflunomide are commonly used synthetic disease-modifying antirheumatic drugs in early rheumatoid arthritis. IFN-γ, interferon-gamma; IL, interleukin; TGF-β, transforming growth factor beta; Th, helper T cell; T reg, regulatory T cell; TNF, tumor necrosis factor; RANKL, receptor activator of nuclear factor kappa-B ligand. Figure adapted with permission from Nakashima and Takayanagi [35] ©Springer.

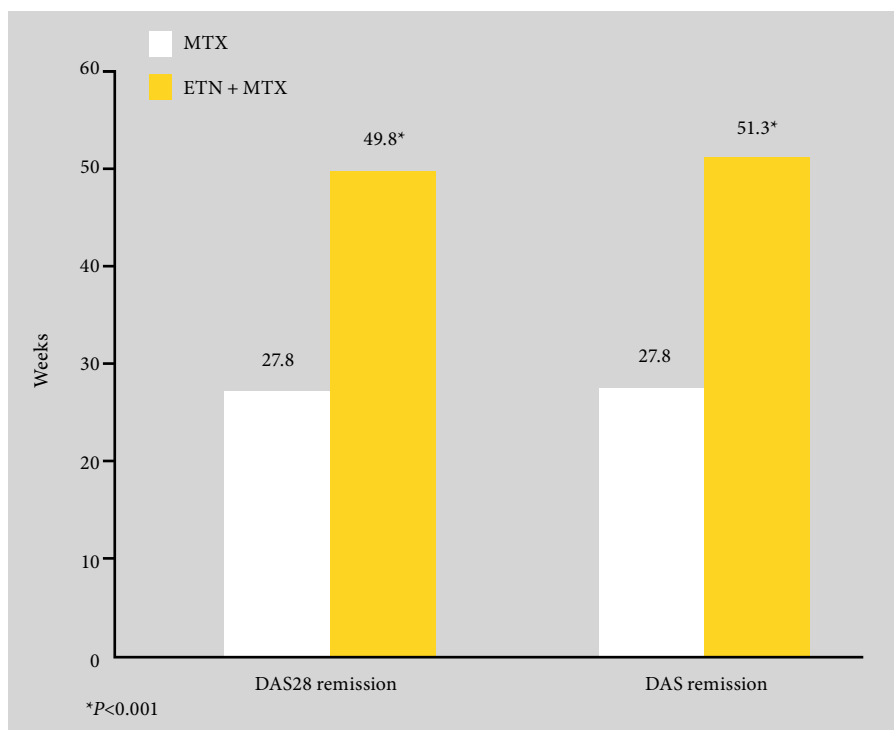


Figure 3.11 Percentage of patients achieving remission at week 52 in the groups receiving methotrexate versus methotrexate plus etanercept in the COMET study. DAS, disease activity score; DAS28, disease activity score in 28 joints; ETN, etanercept; MTX, methotrexate. Reproduced with permission from Emery et al [39]©Lancet.

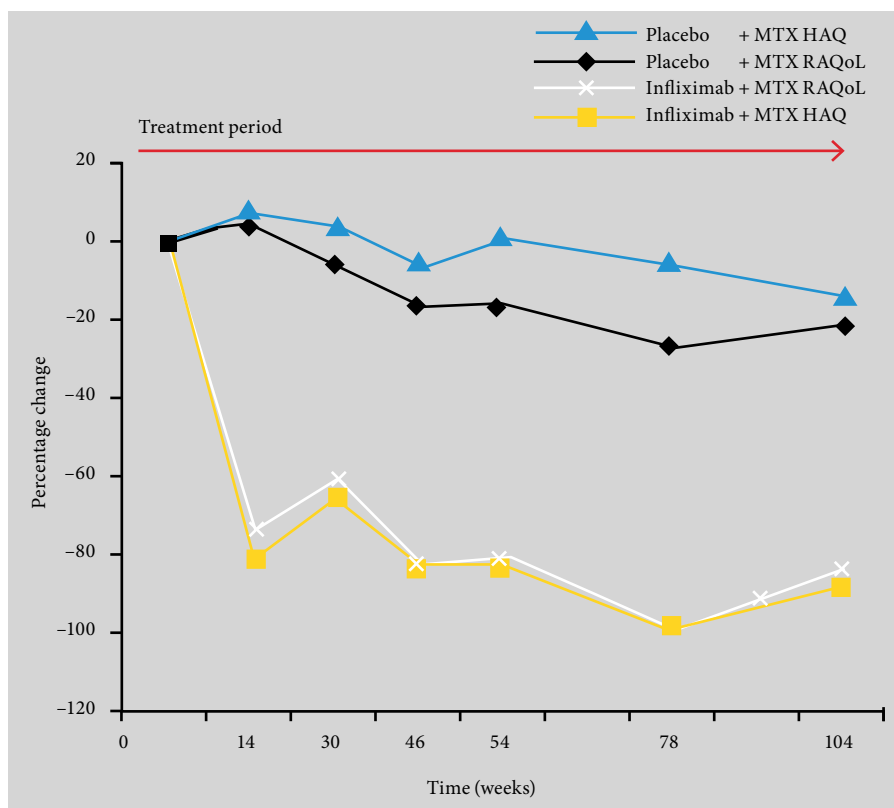


Figure 3.12 Induction with biological and maintenance with synthetic disease-modifying antirheumatic drugs. This figure shows the percentage change in the median functional (by Health Assessment Questionnaire [HAQ]) and quality of life (by the Rheumatoid Arthritis Quality of Life [RAQoL] questionnaire) scores over time in the infliximab-plus-methotrexate (MTX) group and the placebo-plus-MTX group. The functional and quality of life benefits obtained in patients treated with infliximab after one year was sustained at two years without further infliximab infusions. Reproduced with permission from Quinn et al [11] ©Wiley.

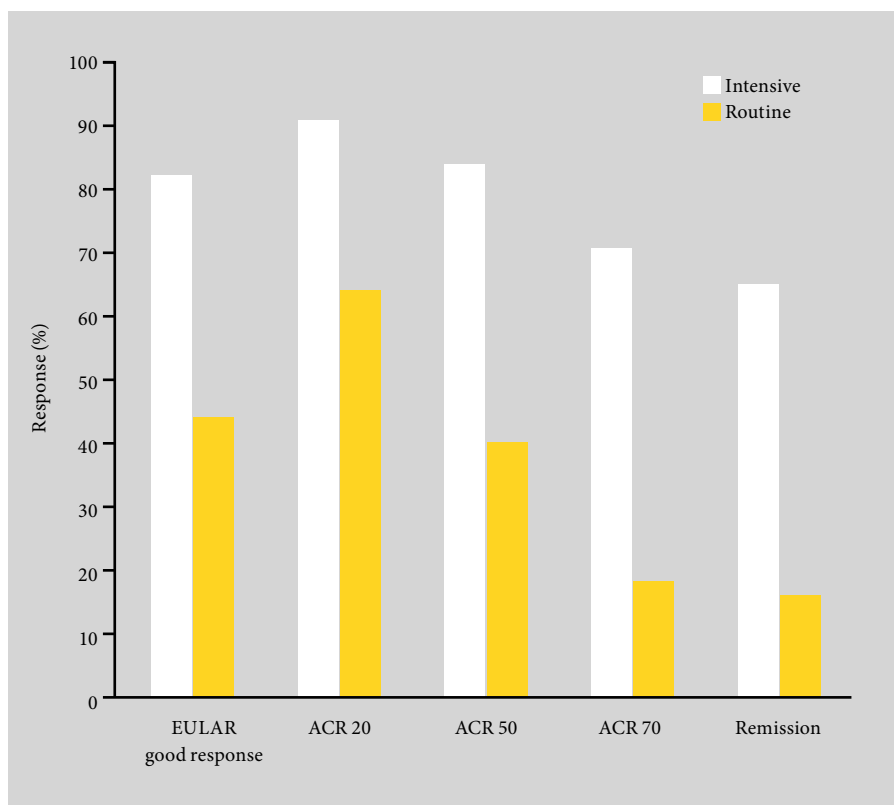


Figure 3.13 Intensive versus routine monitoring: results from the Tight Control in Rheumatoid Arthritis (TICORA) study. In the TICORA study, patients in the intensive treatment group experienced significantly greater EULAR and ACR responses and higher remission rates than the control group after 18 months of follow-up. ACR, American College of Rheumatology; EULAR, European League Against Rheumatism. Reproduced with permission from Grigor et al [42] ©Lancet.

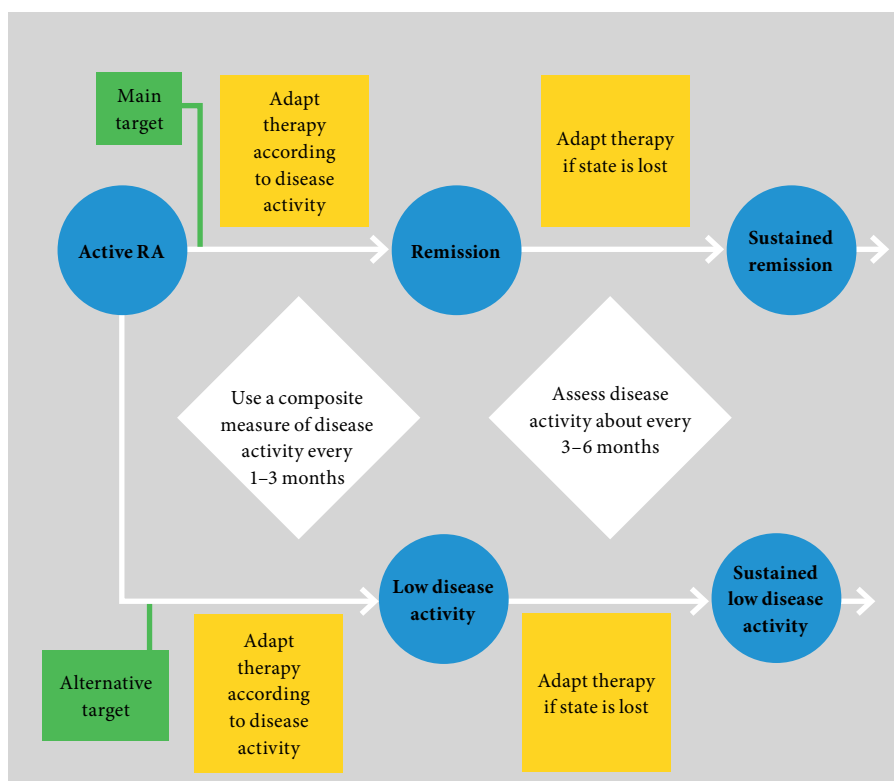


Figure 3.14 Algorithm for treating rheumatoid arthritis to target based on European League Against Rheumatism (EULAR) treat to target recommendations. When monitoring treatment of patients with rheumatoid arthritis (RA), measures of disease activity should be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently (eg, every 3–6 months) for patients in sustained low disease activity or remission. It is suggested that drug therapy should be adjusted at least every 3 months until the desired treatment target is reached. The patient should be appropriately informed about the treatment target and the strategy planned to reach this target under the supervision of the rheumatologist. The desired treatment target should be maintained throughout the remaining course of the disease. Produced with permission from Smolen et al [41] ©BMJ.

Composite measures	Formulas
DAS	DAS (4 variables) $0.54 \times (\sqrt{\text{Ritchie}}) + 0.065 \times (\text{SJC44}) + 0.33 \times \ln(\text{ESR}) + 0.072(\text{general health})$ DAS (3 variables) $0.54 \times (\sqrt{\text{Ritchie}}) + 0.065 \times (\text{SJC44}) + 0.33 \times \ln(\text{ESR}) + 0.224$
DAS28	DAS28 (4 variables) $0.56 \times (\sqrt{\text{TJC28}}) + 0.28 \times (\sqrt{\text{SJC28}}) + 0.70 \times \ln(\text{ESR}) + 0.014(\text{general health})$ DAS28 (3 variables) $0.54 \times (\sqrt{\text{TJC28}}) + 0.28 \times (\sqrt{\text{SJC28}}) + 0.70 \times \ln(\text{ESR}) + 0.016$ DAS28 CRP (4 variables) $0.56 \times (\sqrt{\text{TJC28}}) + 0.28 \times (\sqrt{\text{SJC28}}) + 0.36 \times \ln(\text{CRP}(\text{mg/l}), +1) + 0.014(\text{general health}) + 0.96$
Simplified DAS	$\text{SJC28} + \text{TJC28} + \text{patient global health}(\text{VAS; 0–10}) + \text{physician global}(\text{VAS; 0–10}) + \text{CRP}(\text{mg/dL})$
Clinical DAS	$\text{SJC28} + \text{TJC28} + \text{patient global health}(\text{VAS; 0–10}) + \text{physician global}(\text{VAS; 0–10})$

Table 3.4 Composite disease activity scores used in clinical practice for measuring rheumatoid arthritis disease activity. CRP, C-reactive protein; DAS, disease activity score; DAS28, disease activity score in 28 joints; ESR, erythrocyte sedimentation rate; ln, natural logarithm; Ritchie, Ritchie articular index; SJC28, 28-swollen-joint-count; SJC44, 44-swollen-joint count; TJC28, 28-tender-joint count; VAS, visual analogue scale.

Disease activity scores	Remission	Low	Moderate	High
DAS	<1.6	≤2.4	≤3.7	>3.7
DAS28	<2.6	≤3.2	≤5.1	>5.1
SDAI	≤3.3	< 11	<26	≥26
CDAI	≤2.8	<10	<22	≥22

Table 3.5 Cut-off values for levels of disease activity of various composite measures in rheumatoid arthritis. CDAI, clinical disease activity index; DAS, disease activity score; DAS28, disease activity score in 28 joints; SDAI, simplified disease activity index. Adapted with permission from van der Heijde and Bøyesen [46].

Clinical trial	Treatment groups	Treatment target
FIN-RACo [47–49]	SSZ (mono group) (n=98) vs MTX, SSZ, HCQ and prednisolone (combo group) (n=97)	Improvement in ≥ 2 of 3 criteria (TJC, SJC, and ESR or CRP) Modified ACR remission
BeSt [12,50]	1. Sequential monotherapy (n=126); 2. Step-up monotherapy (n=121); 3. Combination therapy with prednisone (n=133); 4. Combination therapy with IFX (n=128)	LDAS (DAS44 ≤ 2.4)
CAMERA-II [51]	- MTX monotherapy (n=117) - MTX + prednisolone 10mg/d (n=119)	>20% improvement in SJC and ≥ 2 of TJC, ESR, and VAS GH
SWEFOT [52–54]	MTX monotherapy (n=487) (A) If DAS28 ≤ 3.2 after 3–4 months (n=147): - Continue MTX (B) If DAS28 > 3.2 after 3–4 months: - SSZ + HCQ (n=130) vs - IFX (n=128)	LDAS28 (DAS28 ≤ 3.2)
NEO-RACo [55]	MTX, SSZ, HCQ, prednisolone + placebo (n=49) vs MTX, SSZ, HCQ, prednisolone + 6 months of IFX (n=50)	Modified ACR remission

Table 3.6 Randomized controlled trials comparing different treatment combinations together with treat to target strategies in disease-modifying antirheumatic drugs-naïve rheumatoid arthritis. ACR, American College of Rheumatology; CI, confidence interval; CRP, C-reactive protein; LDAS, low disease activity score; DAS28, disease activity score in 28 joints; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; HCQ, hydroxychloroquine; IFX, infliximab; IQR, interquartile range; MTX, methotrexate; NS, not significant; SD, standard deviation; SHS, Sharp/van der Heijde score; SJC, swollen joint count; SSZ, sulfasalazine; TJC, tender joint count; VAS-GH, visual analogue scale of general health.

Clinical outcomes	Radiographic outcomes
ACR remission: 2 years: 18% vs 37%; $P=0.003$ 5 years: 22% vs 28% NS	Median Larsen score: 2 years: 12 (IQR 4–20) vs 4 (0–14); $P=0.002$ 5 years: 24 (10–34) vs 11 (2–26); $P=0.001$ 11 years: 27 (95% CI, 22–33) vs 17 (12–26); $P=0.037$
LDAS44 ($DAS \leq 2.4$): 1 year: 53%; 64%; 71%; 74% $P<0.01$ (1 vs 3 and 1 vs 4) 2 years: 75%; 81%; 78%; 82% NS Drug-free remission: 3 years: 11%; 6%; 7% and 16%; $P<0.05$ (4 vs 2+3)	Median change SHS: 2 years: 2.0 (IQR 0.0–8.6) ; 2.0 (0.3–7.0); 1.0 (0.0–2.5); 1.0 (0.0–3.0); $P=0.005$ (1+2 vs 3+4)
Time to first sustained remission: 11 months: (SD 5) vs 6 months (SD 5) $P<0.001$	Median change in SHS: 2 years 0 (IQR 0–2) vs 0 (0–0); $P=0.022$
EULAR good response: 1 year: 63% vs 65% 2 years: 66% vs 68%	
LDAS28 after 3–4 months 30.1% (A) DAS28 remission: 1 year: 59.6% 2 years: 71.8% (B) EULAR good response: 1 year: 25% vs 39% $P=0.0160$ 2 years: 38% vs 31% NS	(A) Mean change SHS: 2 years 3.90 (SD 6.84) SHS=0 2 years 45.6% (B) Mean change SHS: 2 years 7.23 (SD 12.72) vs 4 (10.05); $P=0.009$ Median increase SHS: 2 years 3 (IQR 0–11.25) vs 1 (0–5); $P=0.009$
Modified ACR remission: 2 years: 53% (95% CI 38–67); vs 66% (51–81) NS Sustained modified ACR remission: 2 years: 10% (95% CI 3–22); vs 26% (15–40); $P=0.042$ Mean DAS28 remission: 2 years: 82% (95% CI 72–93) vs 82% (71–93) NS	Mean change SHS: 2 years: –0.2 (–1.2–0.4) vs 1.4 (0.8–2.3); $P=0.0058$

1. Arthritis is characterized by the presence of joint swelling, associated with pain or stiffness. Patients presenting with arthritis of more than 1 joint should be referred to, and seen by, a rheumatologist, ideally within 6 weeks after onset of symptoms
2. Clinical examination is the method of choice for detecting synovitis. In doubtful cases, ultrasound, power Doppler, and MRI might be helpful to detect synovitis
3. Exclusion of disease other than rheumatoid arthritis requires careful history taking and clinical examination, and ought to include at least the following laboratory tests: complete blood cell count, urinalysis, transaminases, and antinuclear antibodies
4. In every patient presenting with early arthritis to the rheumatologist, the following factors predicting persistent and erosive disease should be measured: number of swollen and tender joints, ESR or CRP, level of rheumatoid factor and ACPA, and radiographic erosions
5. Patients at risk of developing persistent or erosive arthritis should be started with DMARDs as early as possible, even if they do not yet fulfill established classification criteria for inflammatory rheumatologic diseases
6. Patient information concerning the disease and its treatment and outcome is important. Education programs aimed at coping with pain, disability and maintenance of work ability may be employed as adjunct interventions
7. NSAIDs have to be considered in symptomatic patients after evaluation of gastrointestinal, renal, and cardiovascular status
8. Systemic glucocorticoids reduce pain and swelling and should be considered as adjunctive treatment (mainly temporary), as part of the DMARD strategy. Intra-articular glucocorticoids injections should be considered for the relief of local symptoms of inflammation
9. Among the DMARDs, methotrexate is considered to be the anchor drug, and should be used first in patients at risk of developing persistent disease
10. The main goal of DMARD treatment is to achieve remission. Regular monitoring of disease activity and adverse events should guide decisions on choice and changes in treatment strategies (DMARDs including biological agents)
11. Non-pharmaceutical interventions such as dynamic exercises, occupational therapy, and hydrotherapy can be applied as adjuncts to pharmaceutical interventions in patients with early arthritis
12. Monitoring of disease activity should include tender and swollen joint count, patient's and physician's global assessments, ESR and CRP. Arthritis activity should be assessed at one to three month intervals, for as long as remission is not achieved. Structural damage should be assessed by radiographs of hands and feet every 6–12 months during the first few years. Functional assessment (for example, HAQ) can be used to complement the disease activity and structural damage monitoring

Table 3.7 European League Against Rheumatism (EULAR) recommendations on the management of early arthritis. ACPA, anti-citrullinated peptide; CRP, C reactive protein; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; MRI, magnetic resonance imaging; NSAID, non-steroidal anti-inflammatory drugs. Reproduced with permission from Combe et al [60] ©BMJ.

References

1. Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum.* 1998;41:778-799.
2. Symmons D, Turner G, Webb R, et al. The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. *Rheumatology.* 2002;41:793-800.
3. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. *Semin Arthritis Rheum.* 2006;36:182-188.
4. Eriksson JK, Neovius M, Ernestam S, Lindblad S, Simard JF, Askling J. Incidence of Rheumatoid Arthritis in Sweden – a nationwide population-based assessment of incidence, its determinants, and treatment penetration. *Arthritis Care Res (Hoboken).* 2013;65:870-878.
5. Cobb S, Anderson F, Bauer W. Length of life and cause of death in rheumatoid arthritis. *N Engl J Med.* 1953;249:553-556.
6. Solomon DH, Goodson NJ, Katz JN, et al. Patterns of cardiovascular risk in rheumatoid arthritis. *Ann Rheum Dis.* 2006;65:1608-1612.
7. Myllykangas-Luosujarvi RA, Aho K, Isomaki HA. Mortality in rheumatoid arthritis. *Semin Arthritis Rheum.* 1995;25:193-202.
8. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis.* 2010;69:1580-1588.
9. Finckh A, Liang MH, van Herckenrode CM, de Pablo P. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: A meta-analysis. *Arthritis Rheum.* 2006;55:864-872.
10. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis.* 2010;69:964-975.
11. Quinn MA, Conaghan PG, O'Connor PJ, et al. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2005;52:27-35.
12. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum.* 2005;52:3381-3390.
13. Klarenbeek NB, Guler-Yuksel M, van der Kooij SM, et al. The impact of four dynamic, goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the BeSt study. *Ann Rheum Dis.* 2011;70:1039-1046.
14. Boers M, Verhoeven AC, Markusse HM, et al. Randomized comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet.* 1997;350:309-318.
15. Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis.* 2010;69:631-637.
16. Taylor, PC. Antibodies for Inflammatory Disease. In, George AT, Urch CE, eds. *Diagnostic and Therapeutic Antibodies.* Totowa, NJ: Humana Press; 2000.
17. van der Linden MP, le Cessie S, Raza K, et al. Long-term impact of delay in assessment of patients with early arthritis. *Arthritis Rheum.* 2010;62:3537-3546.
18. Breedveld FC, Kalden JR. Appropriate and effective management of rheumatoid arthritis. *Ann Rheum Dis.* 2004;63:627-633.
19. Verpoort KN, van Dongen H, Allaart CF, Toes RE, Breedveld FC, Huizinga TW. Undifferentiated arthritis-disease course assessed in several inception cohorts. *Clin Exp Rheumatol.* 2004;22(5 suppl 35):S12-S17.
20. Combe B, Landewe R, Lukas C, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis.* 2007;66:34-45.

21. Matteson E, Mason T, Hunder G. *Atlas of Rheumatology*. London, UK: Current Medicine Group; 2002.
22. Arthritis Research UK. "Step 1 – recognising symptoms before seeking help." Arthritis UK website. www.arthritisresearchuk.org/arthritis-information/inflammatory-arthritis-pathway/step-one.aspx. Accessed March 6, 2015.
23. Nam JL, Combe B, Emery P. Early arthritis. In: Johannes WJ Bijlsma, ed. *EULAR Textbook on Rheumatic Disease*. London, UK: BMJ Group; 2012:185-205.
24. Wolfe F, Ross K, Hawley DJ, Roberts FK, Cathey MA. The prognosis of rheumatoid arthritis and undifferentiated polyarthritis syndrome in the clinic: a study of 1141 patients. *J Rheumatol*. 1993;20:2005-2009.
25. Tunn EJ, Bacon PA. Differentiating persistent from self-limiting symmetrical synovitis in an early arthritis clinic. *Br J Rheum*. 1993;32:97-103.
26. Bukhari M, Lunt M, Harrison BJ, Scott DG, Symmons DP, Silman AJ. Rheumatoid factor is the major predictor of increasing severity of radiographic erosions in rheumatoid arthritis: results from the Norfolk Arthritis Register Study, a large inception cohort. *Arthritis Rheum*. 2002;46:906-912.
27. Machold KP, Stamm TA, Nell VP, et al. Very recent onset rheumatoid arthritis: clinical and serological patient characteristics associated with radiographic progression over the first years of disease. *Rheumatology (Oxford)*. 2007;46:342-349.
28. Aggarwal R, Liao K, Nair R, Ringold S, Costenbader KH. Anti-citrullinated peptide antibody assays and their role in the diagnosis of rheumatoid arthritis. *Arthritis Rheum*. 2009;61:1472-1483.
29. Meyer O, Labarre C, Dougados M, et al. Anticitrullinated protein/peptide antibody assays in early rheumatoid arthritis for predicting five year radiographic damage. *Ann Rheum Dis*. 2003;62:120-126.
30. Visser H, le Cessie S, Vos K, Breedveld FC, Hazes JM. How to diagnose rheumatoid arthritis early: a prediction model for persistent (erosive) arthritis. *Arthritis Rheum*. 2002;46:357-365.
31. Thabet MM, Huizinga TW, van der Heijde DM, van der Helm-van Mil AH. The prognostic value of baseline erosions in undifferentiated arthritis. *Arthritis Res Ther*. 2009;11:R155.
32. Jansen LM, van der Horst-Bruinsma IE, van Schaardenburg D, Bezemer PD, Dijkman BA. Predictors of radiographic joint damage in patients with early rheumatoid arthritis. *Ann Rheum Dis*. 2001;60:924-927.
33. EULAR Standing Committee on Musculoskeletal Imaging. EULAR database on Imaging in Rheumatology. www.eular.org. Accessed March 6, 2015.
34. Fex E, Jonsson K, Johnson U, Eberhardt K. Development of radiographic damage during the first 5–6 yr of rheumatoid arthritis. A prospective follow-up study of a Swedish cohort. *Br J Rheumatol*. 1996;35:1106-1115.
35. Nakashima T, Takayanagi H. Osteoimmunology: crosstalk between the immune and bone systems. *J Clin Immunol*. 2009;29:555-556.
36. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis*. 2010;69:964-975.
37. Nam JL, Winthrop KL, van Vollenhoven RF, et al. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. *Ann Rheum Dis*. 2010;69:976-986.
38. Schoels M, Wong J, Scott DL, et al. Economic aspects of treatment options in rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis*. 2010;69:995-1003.
39. Emery P, Breedveld FC, Hall S, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomized, double-blind, parallel treatment trial. *Lancet*. 2008;372:375-378.
40. Knevel R, Schoels M, Huizinga TW, et al. Current evidence for a strategic approach to the management of rheumatoid arthritis with disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis*. 2010;69:987-994.

41. Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis.* 2010;69:631-637.
42. Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomized controlled trial. *Lancet.* 2004;364:263-269.
43. Verstappen SM, Jacobs JW, van der Veen MJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). *Ann Rheum Dis.* 2007;66:1443-1449.
44. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: Dimensions and Practical Applications. *Health Qual Life Outcomes.* 2003;1:20.
45. Schoels M, Knevel R, Aletaha D, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search. *Ann Rheum Dis.* 2010;69:638-643.
46. van der Heijde D, Bøyesen P. Measuring disease activity and damage in arthritis. In: Johannes WJ Bijlsma, ed. *EULAR Textbook on Rheumatoid Diseases*. London: BMJ Group; 2012:1107-1134
47. Mottonen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomized trial. FIN-RACo trial group. *Lancet.* 1999;353:1568-1573.
48. Korpela M, Laasonen L, Hannonen P, et al. Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with disease-modifying antirheumatic drugs: five-year experience from the FIN-RACo study. *Arthritis Rheum.* 2004;50:2072-2081.
49. Rantalaiho V, Korpela M, Laasonen L, et al. Early combination disease-modifying antirheumatic drug therapy and tight disease control improve long-term radiologic outcome in patients with early rheumatoid arthritis: the 11-year results of the Finnish Rheumatoid Arthritis Combination Therapy trial. *Arthritis Res Ther.* 2010;12:R122.
50. Allaart CF, Breedveld FC, Dijkmans BA. Treatment of recent-onset rheumatoid arthritis: lessons from the BeSt study. *J Rheumatol Suppl.* 2007;80:25-33.
51. Bakker MF, Jacobs JW, Welsing PM, et al. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. *Ann Intern Med.* 2012;156:329-339.
52. van Vollenhoven RF, Ernestam S, Geborek P, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomized trial. *Lancet.* 2009;374:459-466.
53. van Vollenhoven RF, Geborek P, Forslind K, et al. Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomized, non-blinded, parallel-group Swefot trial. *Lancet.* 2012;379:1712-1720.
54. Rezaei H, Saevarsdottir S, Forslind K, et al. In early rheumatoid arthritis, patients with a good initial response to methotrexate have excellent 2-year clinical outcomes, but radiological progression is not fully prevented: data from the methotrexate responders population in the SWEFOT trial. *Ann Rheum Dis.* 2012;71:186-191.
55. Leirisalo-Repo M, Kautiainen H, Laasonen L, et al. Infliximab for 6 months added on combination therapy in early rheumatoid arthritis: 2-year results from an investigator-initiated, randomized, double-blind, placebo-controlled study (the NEO-RACo Study). *Ann Rheum Dis.* 2013;72:851-857.
56. Klarenbeek NB, Guler-Yuksel M, van der Kooij SM, et al. The impact of four dynamic, goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the BeSt study. *Ann Rheum Dis.* 2011;70:1039-1046.
57. van der Kooij SM, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis. *Ann Rheum Dis.* 2009;68:914-921.
58. Kavanaugh A, Fleischmann RM, Emery P, et al. Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-week results from the randomized, controlled OPTIMA study. *Ann Rheum Dis.* 2013;72:64-71.

59. Soubrier M, Puechal X, Sibilia J, et al. Evaluation of two strategies (initial methotrexate monotherapy vs its combination with adalimumab) in management of early active rheumatoid arthritis: data from the GUEPARD trial. *Rheumatology*. 2009;48:1429-1434.
60. Combe B, Landewe R, Lukas C, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis*. 2007;66:34-45.

4 Established rheumatoid arthritis

Michael Weisman, Thomas J Leach

Introduction

The images presented in this chapter reflect a broad spectrum of clinical manifestations and radiographic images of established rheumatoid arthritis (RA), including some manifestations such as severe deformities that are rarely seen in clinical practice because the clinical presentation of established RA has substantially changed over the last two decades. The change in clinical presentation is largely due to the use of disease-modifying anti-rheumatic drugs (DMARDs), particularly methotrexate, early in the disease course. The effect of DMARDs has been to tame the chronic inflammatory process and delay the progression of RA. In fact, according to classification criteria, the average number of tender and swollen joints was lower among patients classified with RA in 2010 than in 1987 [1]. In recognition of this significant change in the treatment and course of RA, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) recently issued new classification criteria for RA [2]. The 2010 ACR/EULAR classification criteria replaced the 1987 ACR RA classification criteria and are intended to classify RA earlier in the disease course [1]. These new classification criteria are targeted to patients presenting for the first time with at least one swollen joint and swelling not explained by another disease [2]. Four domains are included in an algorithm in which a score of at least 6 out of 10 is required for the classification of RA. The domains are: joint involvement, serology, acute-phase reactants, and duration of symptoms.

The course of RA may be cyclic or aggressively active and the progression and rate at which joint destruction occurs is quite variable [3]. Factors that influence disease progression include rheumatoid factor (RF) production, gender, erosive disease at presentation [4], anti-cyclic citrullinated peptide antibodies (ACPA) [5], C-reactive protein (CRP), human leukocyte antigen (HLA) shared epitope, and baseline radiographic damage [6]. Presentation with arthritis of the knees is also predictive of a more destructive course of RA [7]. Within 3 months following diagnosis, erosive damage will occur in 10–26% of patients. After 2 years, over three-quarters of patients with RA will exhibit some type of erosive joint damage [6].

The characteristic features of RA are expressed in articular and periarticular manifestations of the upper and lower extremities. Swelling of the metacarpophalangeal (MCP) joints is one of the hallmark signs of RA and one that distinguishes RA from osteoarthritis even in its inflammatory form. The majority of patients with RA will also experience wrist involvement at some point during the course of their disease; up to 50% within the first two years of disease onset [5]. Elbow and shoulder symptoms appear in about one-third of cases [5]. Among the lower extremities, over 90% of patients exhibit signs and symptoms in the knees, ankles, and feet; the hips tend to be less frequently involved. In addition to articular and periarticular manifestations of the upper and lower extremities, 17–88% of patients may experience cervical spine abnormalities, although the prevalence of these abnormalities is on the decline due to aggressive, early treatment [5].

Extra-articular manifestations of RA may occur in any of the major organ systems: cardiovascular, pulmonary, ocular, neurologic, skin, hematologic, renal, and hepatic [8]. The incidence and prevalence of any given extra-articular manifestation is variable. The most frequent extra-articular manifestation is rheumatoid nodules, with an estimated 30–40% of all patients developing rheumatoid nodules at some point in their lifetime [9]. In a community-based study of the incidence of RA, the most common extra-articular manifestations were rheumatoid nodules, secondary Sjögren's syndrome, and pulmonary fibrosis [10].

Several imaging modalities are available with which to assess the presence and extent of damage associated with RA. These modalities include radiographic examination, ultrasonography (US), magnetic resonance imaging (MRI), and computed tomography (CT). Radiographs are used to determine the extent of cumulative joint damage [11] and establishing therapeutic response. They may also serve as surrogate indicators of functional disability [12]. Radiography has the advantage of being low-cost and readily accessible. On the other hand, the

disadvantages include its two-dimensional representation of a three-dimensional condition [11,12], failure to assess synovitis and other soft-tissue changes [13], and poor sensitivity in identifying bone erosions [14]. US overcomes the limitations of radiography in that it allows the visualization of a three-dimensional plane as well as soft-tissue lesions and early erosive bone lesions [15]. That said, US has its own limitations including reproducibility of findings (for example, inter- and intra-observer reliability and inter-machine reliability), validity, and responsiveness to change [16].

MRI is an extremely sensitive imaging modality that provides exceptional detail of the bone and surrounding soft tissue as well as erosive damage [17]; specifically, the synovial membrane, intra- and extra-articular fluid collections, cartilage, bone, ligaments, tendons, and tendon sheaths [11]. MRI has yet to be adopted for routine clinical assessment in RA due to its high cost, restricted availability, and exam time [11]. CT is another excellent tool for visualizing the joints and other structures; however, it does not do an adequate job of visualizing soft-tissue changes of articular structure [13]. The use of CT, though, is relatively limited in clinical practice.

Stages of established rheumatoid arthritis

In its beginning stages, established RA is identifiable by the swollen MCP, proximal interphalangeal (PIP), and distal interphalangeal (DIP) joints. The swelling in these joints represents a combination of synovial hypertrophy and exudative synovial fluid all together commonly known as synovitis. Joints with synovitis will be warm and soft to the touch with a fluctuant sensation resulting from the increased tissue and fluid at the site of inflammation. Figure 4.1 displays what is called ‘fusiform’ swelling of the PIP joints (spindle-shaped swelling mostly on the medial and lateral sides of the joint where there are no tendons). Synovitis can be confirmed on physical examination by carefully squeezing the joints or moving them through a normal range of motion and asking the patient to verbalize any pain or discomfort. In addition, Figure 4.1 reveals some of the early changes of established RA such as radial deviation at the wrist, loss of the normal contours of the wrist articulations, and splaying laterally of the digits making the fingers appear spread out. All of these changes are created by pressure from the accumulated synovial hypertrophy and fluid accumulation in the joints.

Figure 4.2 shows signs of radiographic erosions in the second MCP. In the past, treatment has focused on arresting or even preventing this type of bony destruction with early

institution of combinations of drugs that include biologic agents. Figure 4.3 is also indicative of early destructive arthritis including joint space narrowing and radial deviation at the wrist.

Foot and ankle manifestations occur in almost all patients with established RA, with the forefoot being one of the more frequently affected sites and the fifth metatarsophalangeal (MTP) often the first involved joint (Figure 4.4). Foot symptoms occur initially in approximately 13% of patients and may be the presenting manifestation [18]. Ultimately, up to 90% of patients will experience foot and ankle symptoms sometime during the course of their disease [19]. Synovial and soft tissue inflammation causes the foot to swell (Figure 4.5; Figure 4.6) and wearing covered shoes becomes uncomfortable. Patients with RA in the forefoot will report pain while walking and often they will attempt to find larger size shoes not knowing the cause of the problem. Upon physical examination, the MTP joints will feel swollen and display tenderness with compression laterally across the forefoot (the 'squeeze-test' for forefoot arthritis). Given the options available for RA management today (eg, methotrexate, biological agents), it is unusual for patients to spend very much time in this setting of extreme inflammation in the forefeet. Arthritis mutilans is an example of forefeet deformities seen prior to the use of biological agents (Figure 4.7).

With ongoing inflammation, synovial thickening and hypertrophy become more pronounced and joint deformities begin to be clearly visible. In Figure 4.8, for example, we see synovial thickening as well as the beginning of subluxation of the MCP joints. Radiographic evidence of ulnar deviation as well as synovial thickening can be seen in Figure 4.9. A more complete picture of the rheumatoid process via MRI is demonstrated in Figure 4.10.

Deformities associated with disease progression include radial deviation of the wrist (straightening of the ulnar side of the hand and wrist) and the beginning of the ulnar deviation of the digits (Figure 4.8). Upon physical examination and palpation, the joints will feel swollen and warm with the patient noting tenderness. Up to 55% of patients with RA will experience tenosynovitis (inflammation of the synovial fluid-filled sacs that surround the tendon sheaths) along the flexor or extensor digital tendons [20]. In order, the most frequently affected tendons are the third flexor tendon, the second flexor tendon, and the fourth flexor tendon.

As established disease progresses, characteristic changes take place, where the MCP joints appear prominent, firm swelling takes place at the PIP joints where flexion deformities exist,

and muscle atrophy is present on the dorsum of the hand revealing the tendons sitting just under the skin (Figure 4.11). Firm ‘ropy’ appearing swelling may place along the distal ulna on both hands; in Figure 4.11, prominent swelling is present at the MCP and PIP joints of the thumbs, especially in this patient’s right hand. However, joint destruction in RA is not limited to the hands and feet. The knees are frequently sites of inflammation and patients with inadequately managed RA are also susceptible to progressive cartilage damage, ligamentous laxity, and quadriceps muscle atrophy. Figures 4.12 and 4.13, a radiograph and an MRI of the knee in the same patient, illustrate severe muscle atrophy and cartilage loss. From a diagnostic and therapeutic perspective, it is imperative for the clinician to aggressively manage inflammation in the rheumatoid knee in order to avoid producing irreversible cartilage loss and bone destruction resulting in functional disability.

Rheumatoid nodules at the DIP, PIP, and MCP joints develop in 20–35% of patients with RA (Figure 4.14) [9]. Nodules are a symptom of long-standing, active RA. Factors associated with the development of nodules, which may or may not be painful, include cigarette smoking, positive RF, and use of methotrexate. Extra-articular manifestations in the lungs, eyes, and blood vessels occur less commonly but will take place often in conjunction with rheumatoid nodules. Subluxation of the MCP joints, radial deviation at the wrist, and ulnar drift of the fingers are especially prominent in the left hand of the patient displayed in Figure 4.14.

Another clinical sign is present in Figure 4.14 where the patient’s left hand ring finger contains a wedding band that is very unlikely to be removed due to a Boutonniere deformity. This deformity results from slippage of the extensor tendons (which normally extend the MCP joint) down along the side of the MCP joint and, instead of extension, produces flexion of this joint with concomitant extension of the PIP joint.

In Figure 4.15, the patient’s left and right hands represent all of what we want to avoid – the late consequences of disease (including the overuse of steroids), which commonly were seen before the advent of aggressive management of early stages of RA. Here we see nodules everywhere, including the soft tissues of the tips of the thumbs, straightening of the ulnar border of the wrist (likely from destructive changes in the carpus), and marked synovial thickening and early subluxation at the MCP joints, especially in the right hand. In addition, there are lateral deviations and deformities of the PIP joints, volar subluxation at the wrist,

and thinning of the skin with a dermal hemorrhage in the patient's right hand, little finger, likely as a result of minor trauma (typically called 'steroid purpura').

Classic late-stage manifestations of RA, including hyperextension of the PIP joint of the thumb, subluxation at the MCP joints, and swan-neck deformities, including the typical 'Z' or zigzag deformity of the hand (so commonly seen in the 1960s and 1970s), can be seen in Figure 4.16. Chronic swelling of the PIP joint loosens the volar plate causing torn ligaments and hyperextension of the PIP joint. This hyperextension causes the extensor tendon of the DIP joint to hyperflex, resulting in the appearance of a swan's neck. With the early institution of combinations of aggressive therapy, including the use of biologic drugs, the prevalence of these manifestations has significantly declined.

With loss of mobility of the PIP joints and the hyperextension deformity of the thumb, grasp and pinch are severely compromised. The very late stages of this type of hand results in a 'paddle,' which provides very little in the way of hand function. It is really not known how this deformity arises – several theories have been put forward but the most appealing one comes from radiographic evidence. It appears that the navicular bone at the wrist rotates, causing the wrist to deviate towards ulnar side. Biomechanical forces then come into play during normal hand function and subsequently cause a compensatory movement of the fingers toward the radial side, producing the zigzag deformity as in this patient.

Common clinical presentations

Ocular manifestation

Episcleritis, inflammation of the membrane covering the sclera, occurs in less than 10% of patients with RA [21]. It is typically acute in onset, benign, and self-limiting. Episcleritis presents with a sectoral injection of the episcleral and overlying vessels; in some cases, the redness may be diffuse while in others there may be a translucent white nodule in the center of the inflamed area (Figure 4.17). The cornea is generally not affected. However, dellen formation may result from long-standing or recurrent episcleritis. In most cases, episcleritis will resolve spontaneously within 2 or 3 weeks. Patients report the condition as uncomfortable rather than painful. A regimen of topical anti-inflammatory agents and lubricants may be used to alleviate uncomfortable symptoms.

Nodules

Rheumatoid nodules were formerly ubiquitous in a rheumatology practice; now they are rarely seen (Figure 4.18). They still are the most common form of extra-articular manifestations of RA visible to the clinician on physical examination. They occur most frequently on pressure points such as the proximal forearm near the ulnar bone, the Achilles tendon, or on the anterior surface of the proximal tibia where one kneels down. They are usually attached to the bone periosteum or simply float free in the soft tissues. Histologically, they are a granuloma with a characteristic organizing structure, yet there are very few studies of the initial stages of a nodule before the classic fibrotic picture emerges. It is thought that the original nidus is a vasculitis, but the evidence for this is not secure. They have been described to occur just about everywhere in the body including in internal structures such as the heart, lungs, scleral coat of the eye, and dura.

Vasculitis

Figures 4.19 to 4.22 represent most of the various forms of vasculitis that would occur in RA and that would be visible to the clinician on physical inspection. Figures 4.20 and 4.21 represent more widespread findings of vasculitis in the skin including dermal infarctions and small infarcted areas on top of the dermal nodules.

The pathogenesis of these infarctions represents vasculitis in a variety of blood vessels. If the process involves larger arteries such as the digital arteries of the feet (Figure 4.22), patients may present with gangrene of the toes. Typically, the periungual and the dermal infarctions come from necrotizing vasculitis in small post-capillary venules, but the process may involve small arterioles as well as larger medium-sized blood vessels producing rather large areas of ischemia (Figure 4.22). Rarely do we see these lesions today because RA is generally managed early with effective agents and the prevalence of the major triggering event for vasculitis – cigarette smoking – has fortunately been greatly reduced.

Spine and axial joints

Several factors contribute to the risk for cervical spine abnormalities, including multiple and severe peripheral joint involvement, rheumatoid nodules, high-titer RF seropositivity, high-dose steroid treatment, long disease duration, radiographic erosions in hands and feet,

extra-articular features, and vasculitis [22,23]. Fortunately, the presence of cervical spine abnormalities has declined as a result of aggressive treatment. Examples of atlantoaxial subluxation are shown in Figures 4.23 and 4.24. These abnormalities may or may not be symptomatic, and it is generally assumed that the erosive process itself leaves sufficient room in the spinal canal such that the cord is not compressed. However, patients with cervical spine abnormalities may be at risk during anesthesia if the physician is not aware of the problem and the head and neck are manipulated without regard to the underlying process.

Figures 4.25 and 4.26 reveal the consequences of long-standing disease as it affects the hip joint. Figure 4.25 represents RA hip disease itself with symmetric narrowing of the hip joint with erosive disease on the patient's left side, while Figure 4.26 is an example of insufficiency fractures that can occur in patients with RA who become dependent on chronic corticosteroid therapy. Fortunately, this latter complication could become a thing of the past if we continue on the trajectory of treating patients early and aggressively with biologic and nonbiologic DMARDs and avoiding long-term steroid regimens.



Figure 4.1 Early stages of established rheumatoid arthritis. Pictured here is radial deviation at the true wrist joint (seen best on the patient's left hand), fusiform (side-to-side) swelling of the proximal interphalangeal joints, and loss of the normal pinching in of the wrist at the distal radius and ulna articulations with the carpus. The increased fluid accumulation associated with synovial membrane hypertrophy causes the wrist to lose its normal contour and the metacarpal heads at the metacarpophalangeal joints to move laterally making the digits appear spread out.



Figure 4.2 Early rheumatoid arthritis involving second metacarpophalangeal joint. This posteroanterior (PA) radiograph demonstrates diffuse second metacarpophalangeal joint space narrowing with erosions of the radial aspect of the metacarpal head and second proximal phalanx – the classic rheumatoid erosion in its phenotypic appearance, location, and significance.



Figure 4.3 Early destructive rheumatoid arthritis. Posteroanterior radiographs of hands demonstrate bilateral pancarpal and second metacarpophalangeal (MCP) and left third MCP joint space narrowing. Early erosive change of the radial aspect of the left third metacarpal head is present in the left hand (**a**). The typical finding of radial deviation at the wrist is seen in both hands (**a** and **b**) with the ulnar side of the hand appearing as if it is a straight line. The reasons behind this particular deformity are not known, but it is speculated that the navicular bone will rotate due to the synovitis and perhaps destruction of the ligaments in this area; this rotation of the navicular will result in the rotation of the wrist seen in both hands of this patient.

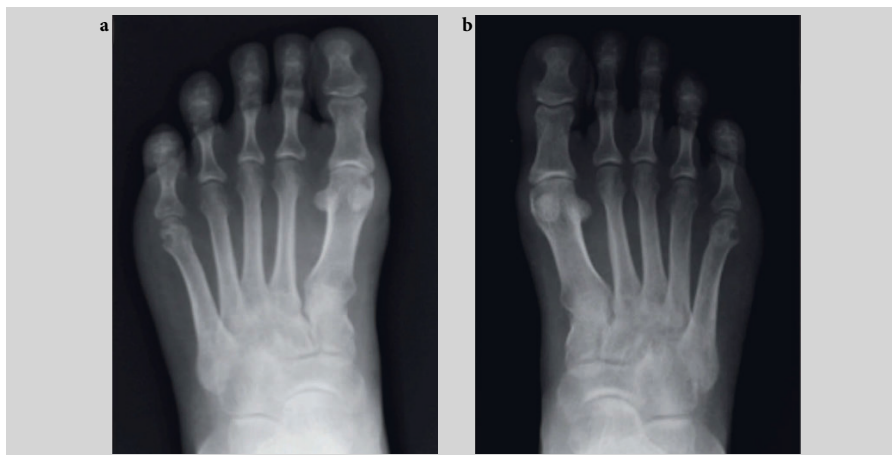


Figure 4.4 Early erosive rheumatoid arthritis of the feet. Posteroanterior radiographs demonstrate erosions of the fifth metatarsal heads bilaterally and symmetrically (**a** and **b**). There is diffuse inflammatory joint space narrowing of the first and fifth metatarsophalangeal joints. Although these erosions do appear corticated in places, they are not to be confused with gouty lesions since other signs in the feet (joint space narrowing elsewhere) are more consistent with rheumatoid arthritis.



Figure 4.5 Established rheumatoid arthritis in metatarsophalangeal joints. Under normal circumstances our toes touch each other; this patient displays the 'daylight sign,' in which the toes splay laterally and daylight is seen between the toes. This occurs when synovial inflammation causes the metatarsal phalangeal joints to spread apart and move away from each other.

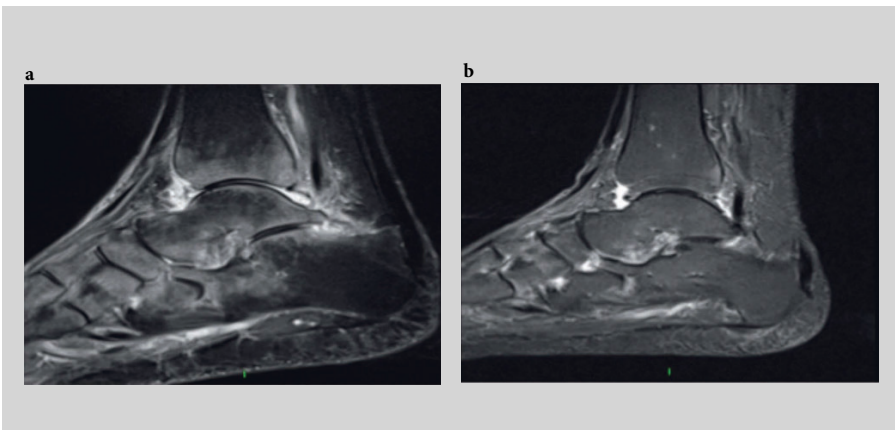


Figure 4.6 Newly diagnosed rheumatoid arthritis and its follow-up 2 years later. Sagittal T2 with fat saturation images obtained in March 2009 (a) and April 2011 (b). At the time of diagnosis, there is marked periarticular bone marrow edema involving hind and mid-foot joints. Ankle effusion is present. Subsequent imaging demonstrates resolution of bone marrow edema and only a small ankle joint effusion. Diffuse hindfoot disease is represented by this case with very active inflammation seen in the early image, while resolution is present in the later imaging study.



Figure 4.7 Arthritis mutilans. Posteroanterior radiographs of feet demonstrate advanced erosive disease of the metatarsophalangeal joints with 'licked candystick' appearance of distal metatarsals, resulting in arthritis mutilans deformities. This situation was commonplace many years ago when patients were not treated early and aggressively for rheumatoid arthritis and the results were these devastating forefeet deformities. Today, rheumatologists are not regularly faced with these clinical situations; in the past, patients had to place metatarsal bars on the bottom of their shoes to avoid weight bearing directly onto these destroyed joints.



Figure 4.8 Mid-rheumatoid arthritis with dramatic synovitis. This patient is exhibiting a straightening of the ulnar border, marked thickening of the synovial tissues at the dorsum of the wrist, mild flexion deformities of the proximal interphalangeal joints and what is likely the beginning of subluxation of the metacarpophalangeal joints where the bases of proximal phalanges move palmar to the metacarpal heads.

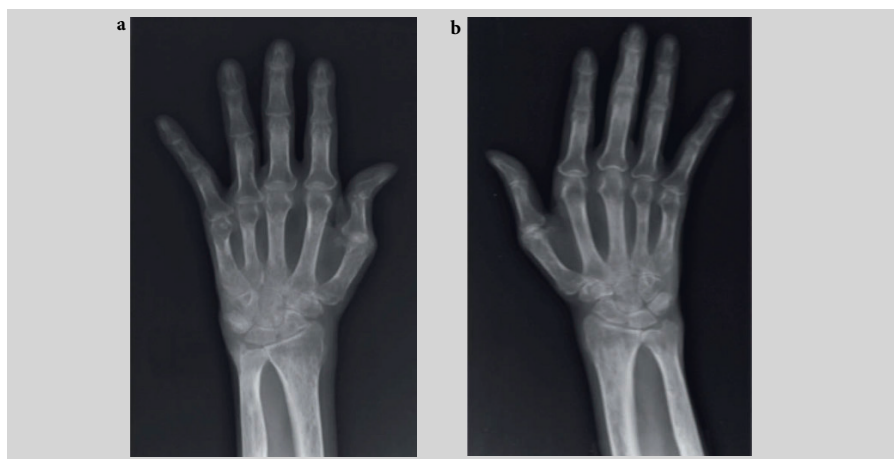


Figure 4.9 Posteroanterior radiograph of hands demonstrate erosive disease at bilateral ulnar styloids. Diffuse inflammatory joint space narrowing of the metacarpophalangeal (MCP) joints is present: (a) greater than (b). As the rheumatoid process becomes more established and destructive, one sees the subsequent ulnar deviation of the fingers at the MCP joints, as well as the radial deviation at the wrist. The reason for this has not been clearly established – perhaps the ulnar drift of the fingers is a mechanical compensation for the radial deviation at the wrist. The bones of this patient are clearly less mineralized and one does see the beginnings of a Boutonnière deformity of the thumb in the left hand.

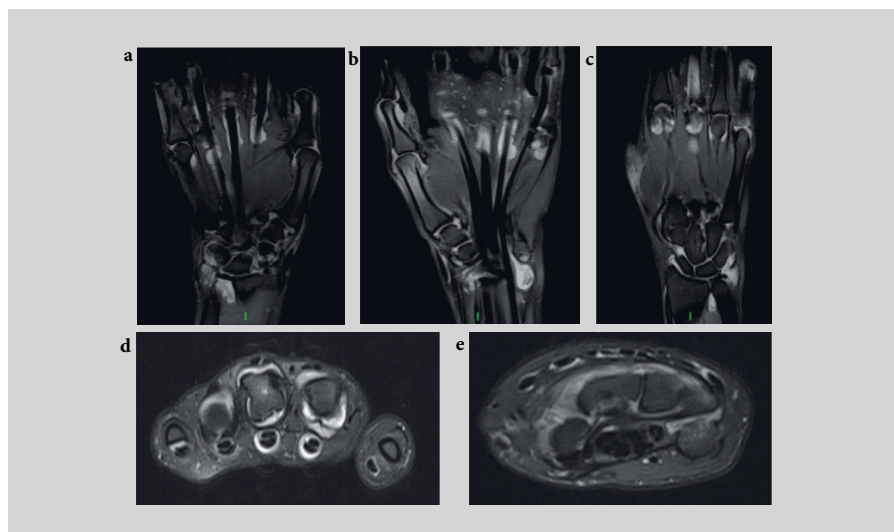


Figure 4.10 Coronal and axial inversion recovery magnetic resonance images (MRI) of bilateral hands. This MRI demonstrates synovitis and effusion of carpal and metacarpophalangeal joints (a–c), as well as tenosynovitis of flexor tendons (d, e). The MRI gives us a more complete picture of the rheumatoid process by revealing the degree of inflammation present in the tendon compartments and surrounding structures. Although the clinician sees the swollen hand and the patient feels pain diffusely in the hand, these images demonstrate the extent of involvement of both joints as well as tenosynovial structures throughout the hand and wrist.



Figure 4.11 Progressive rheumatoid arthritis with metacarpophalangeal and wrist disease. The patient's left hand displays an early deformity of the wrist where the carpal bones move downwards towards the palmar side of the hand indicating volar subluxation of the true wrist joint at the distal ulna and radius. It would be expected that a marked limitation of the usual ranges of motion would be present in this individual, especially at the wrist, metacarpophalangeal, and proximal interphalangeal joints.

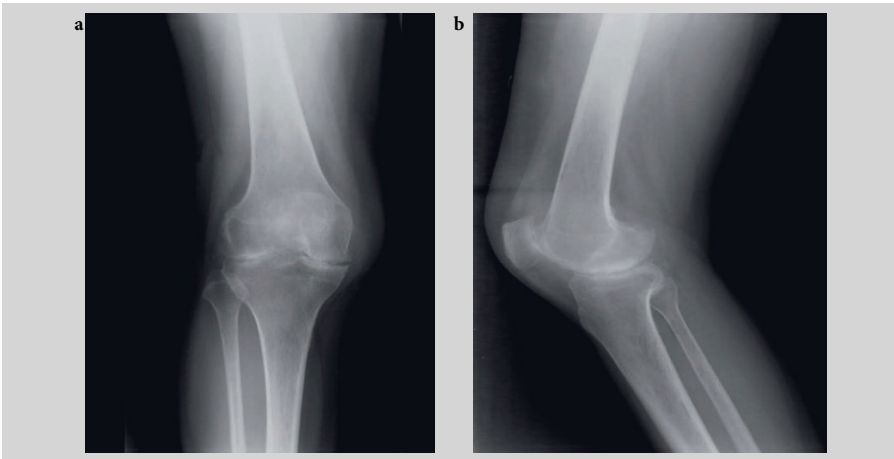


Figure 4.12 Posteroanterior (a) and lateral (b) radiographs of the knees demonstrate diffuse tricompartamental joint space narrowing with suprapatellar effusion. Marked muscle atrophy is noted in the quadriceps of both legs and the degree of widespread cartilage loss is very striking.

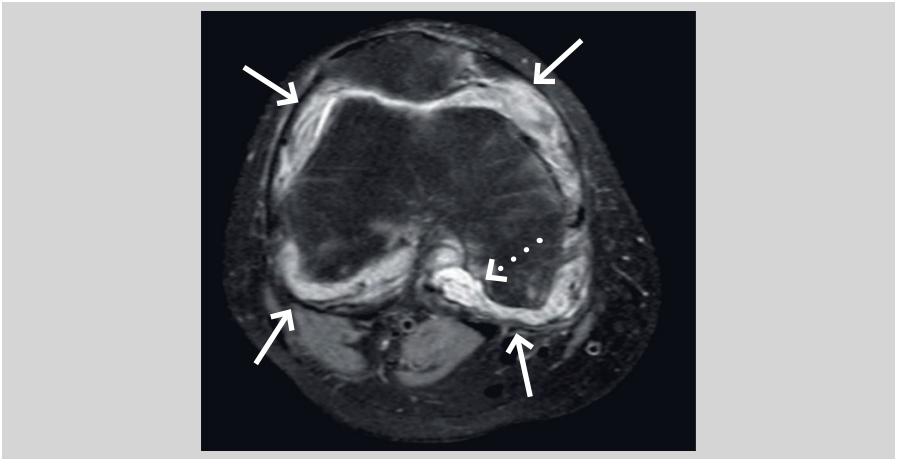


Figure 4.13 Axial proton density with fat saturation image. This patient's image displays effusion and synovitis of the knee joint (arrows) with areas of erosion (dotted arrow) and subchondral bone marrow edema.



Figure 4.14 Late rheumatoid arthritis with deformities and nodules. Hyperextension of the proximal interphalangeal joint and a flexion contracture at the metacarpophalangeal joint in the patient's right thumb, caused by slippage of the extensor tendons, produces what is commonly referred to as a Boutonnière deformity.



Figure 4.15 Late rheumatoid arthritis with nodules and deformities. Consequences of late-stage rheumatoid arthritis include nodules that permeate the soft tissues and deformities in the proximal interphalangeal and metacarpophalangeal joints. Also seen on the patient's right hand is a thinning of the skin with a dermal hemorrhage.



Figure 4.16 Late rheumatoid arthritis with deformities. These deformities truly represent significant functional disability especially regarding fine manipulation of the fingers so necessary for usual activities of daily living.

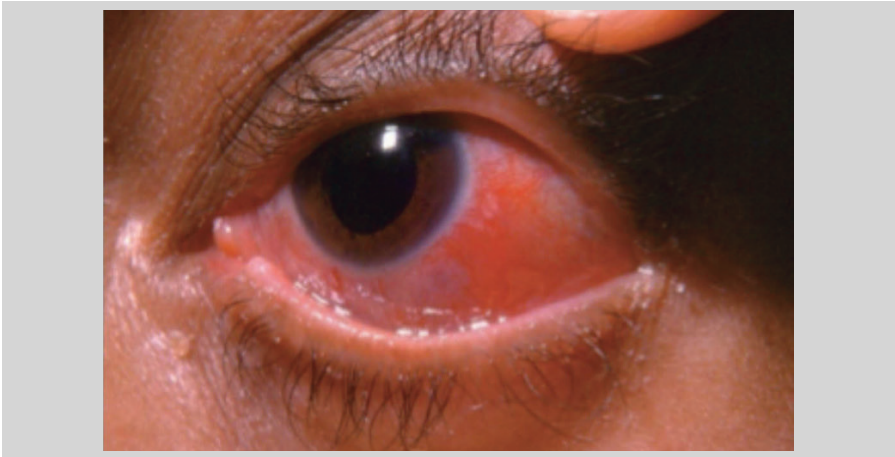


Figure 4.17 Episcleritis in rheumatoid arthritis. Episcleritis (inflammation between the conjunctiva and the sclera) is a localized patch of redness that may be either diffuse or translucent with a white nodule in the middle of the inflamed area. The example in this figure is of diffuse presentation. Vision is usually not affected.

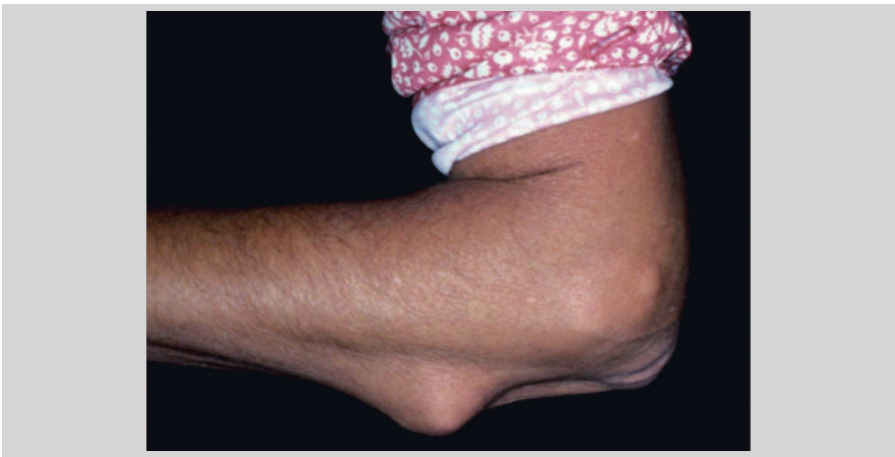


Figure 4.18 Rheumatoid arthritis nodule, typical location. The elbow is a typical location for rheumatoid arthritis nodules. Other typical locations include pressure points in the hands, fingers, Achilles tendons, and knuckles. Nodules may be fixed or movable depending on whether they arise from the periosteum or from the soft tissues of a bursa.

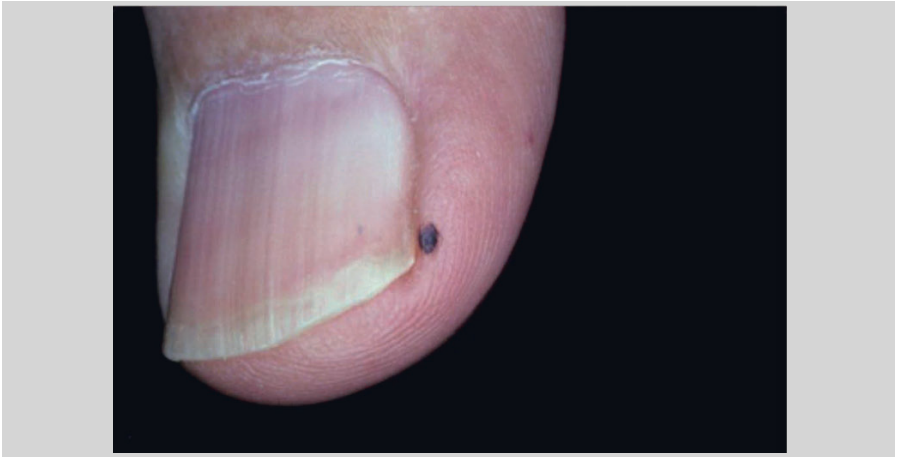


Figure 4.19 Rheumatoid vasculitis – periungual infarct. This is a periungual infarction, a tiny black dot right at the corner where the distal nail touches the skin. This small infarct is typically not even noticed by the patient or thought to be caused by minor trauma. It is usually, but not always, asymptomatic. These periungual infarcts may occur anywhere on the skin next to the nail.



Figure 4.20 Cutaneous vasculitis in rheumatoid arthritis. Multiple dermal infarctions are visible on the fingers of this patient. Dermal ischemia is one of several manifestations of rheumatoid vasculitis.



Figure 4.21 Vasculitis and nodules with infarcts. This patient exhibits multiple symptoms of advanced disease including nodules and cutaneous infarctions on top of the nodules.



Figure 4.22 Late-stage arteritis in rheumatoid arthritis. This patient is presenting with gangrene of the toes as a complication of rheumatoid arthritis-related vasculitis.

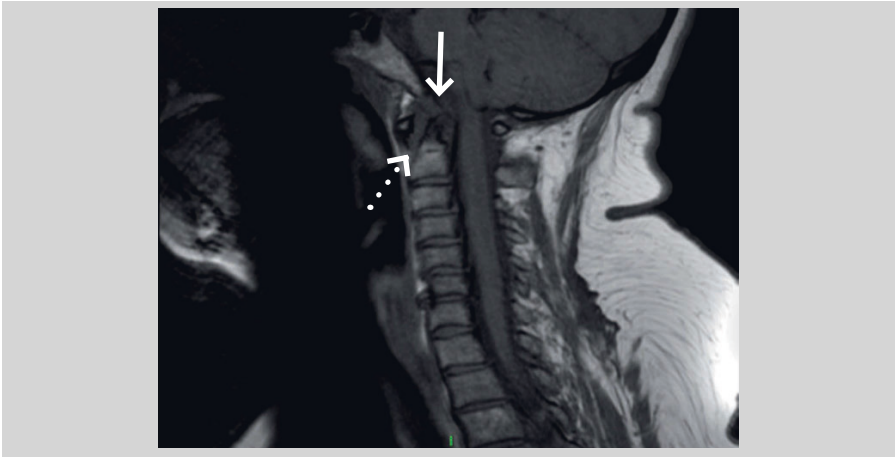


Figure 4.23 Atlantoaxial subluxation. Sagittal T1 magnetic resonance imaging (MRI) demonstrates widening of the distance between the anterior arch of C-1 and the dens (dotted arrow). There is erosion of the dens with a pointed configuration (arrow).

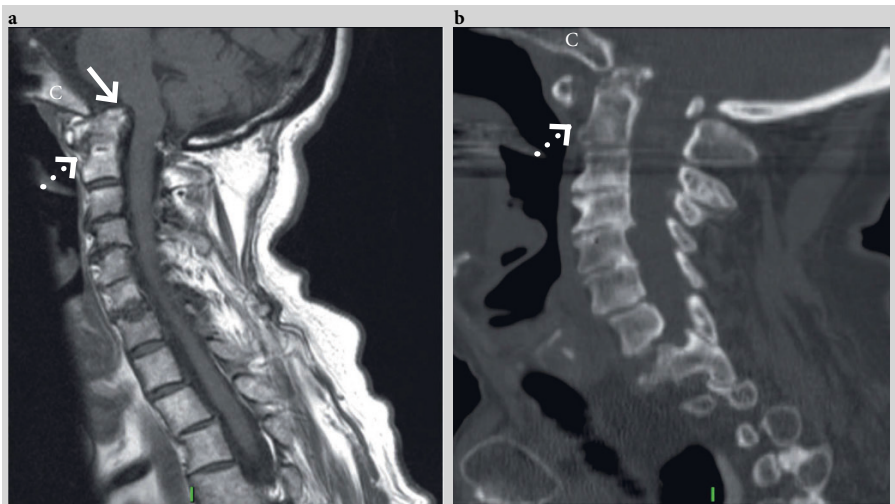


Figure 4.24 Basilar invagination and atlantoaxial subluxation. Sagittal T1 (a) and sagittal computed tomography (CT) (b) demonstrate classic findings of basilar invagination with the dens located cephalad and posterior to the tip of the clivus (C). The dens (arrows) indents the brainstem anteriorly on the left magnetic resonance image. There is widening of the distance between the anterior arch of C-1 and the dens which is seen clearly on the CT image (dotted arrows) (b).



Figure 4.25 Anterior-posterior pelvis radiograph with diffuse bilateral hip joint space narrowing left greater than right. Erosive change is present in the left femoral head. Although radiographs usually demonstrate bilateral and symmetric disease in hands and feet, asymmetric disease can be seen large joints. These findings are clearly distinguishable from osteoarthritis because the migration of the femoral head occurs centrally and diffusely, especially on the right side of this patient.

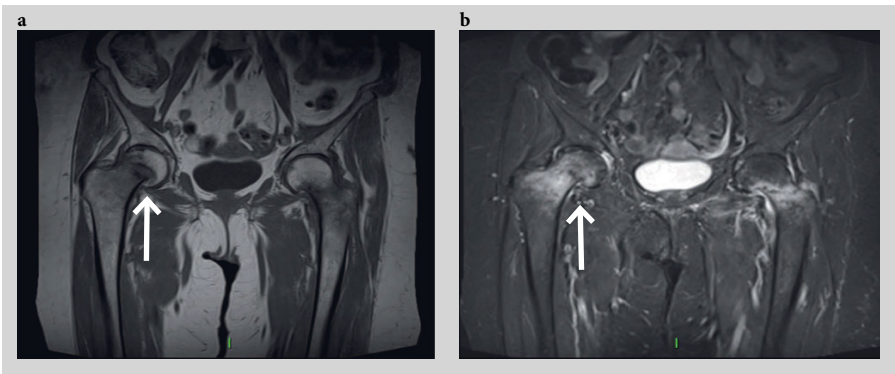


Figure 4.26 Bilateral insufficiency fractures of femoral necks. This woman has been taking corticosteroids for many years and presented with proximal leg pain which was actually referred pain from the fractures of the hips. The MRI reveals fracture lines of the right femoral neck (arrow) with bone marrow edema and impaction (a). On the left side, similar findings are present without definite impaction or displacement (b).

References

1. van der Helm-van Mil AH, Huizinga TW. The 2010 ACR/EULAR criteria for rheumatoid arthritis: do they affect the classification or diagnosis of rheumatoid arthritis? *Ann Rheum Dis.* 2012;71:1596-1598.
2. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum.* 2010;62:2569-2581.
3. Smolen JS, Aletaha D, Grisar J, et al. The need for prognosticators in rheumatoid arthritis. Biological and clinical markers: where are we now? *Arthritis Res Ther.* 2008;10:208.
4. Kaltenhäuser S, Wagner U, Schuster E, et al. Immunogenetic markers and seropositivity predict radiological progression in early rheumatoid arthritis independent of disease activity. *J Rheumatol.* 2001;28:735-744.
5. Posalski J, Weisman MH. Articular and periarticular manifestations of established rheumatoid arthritis. In: Hochberg MC, ed. *Rheumatoid Arthritis*. 1st edn. Philadelphia: Mosby; 2009:49-61.
6. Soubrier M, Dougados M. How to assess early rheumatoid arthritis in daily clinical practice. *Best Pract Res Clin Rheumatol.* 2005;19:73-89.
7. Linn-Rasker SP, van der Helm-van Mil AN, Breedveld FC, Huizinga TW. Arthritis of the large joints – in particular, the knee – at first presentation is predictive for a high level of radiological destruction of the small joints in rheumatoid arthritis. *Ann Rheum Dis.* 2007;66:646-650.
8. Grassi W, DeAngelis R, Lamanna G, Cervini C. The clinical features of rheumatoid arthritis. *Eur J Radiol.* 1998;27(suppl 1):S18-S24.
9. Nyhäll-Wahlin B, Jacobsson LT, Petersson IF, et al. Smoking is a strong risk factor for rheumatoid nodules in early rheumatoid arthritis. *Ann Rheum Dis.* 2006;65:601-606.
10. Turesson C, O'Fallon WM, Crowson CS, et al. Extra-articular disease manifestations in rheumatoid arthritis: Incidence trends and risk factors over 46 years. *Ann Rheum Dis.* 2003;62:722-727.
11. Østergaard M, Pedersen SJ, Døhn UM. Imaging in rheumatoid arthritis: Status and recent advances for magnetic resonance imaging, ultrasonography, computed tomography and conventional radiography. *Best Pract Res Clin Rheumatol.* 2008;22:1019-1044.
12. van der Heijde D. Radiography. In: Hochberg MC, Silman AJ, Smolen JS, eds. *Rheumatoid Arthritis*, 1st edn. Philadelphia: Mosby; 2009: 260-266.
13. Østergaard M, Ejbjerg B, Szkudlarek M. Imaging in early rheumatoid arthritis: Roles of magnetic resonance imaging, ultrasonography, conventional radiography and computed tomography. *Best Pract Res Clin Rheumatol.* 2005;19:91-116.
14. Døhn UM, Ejbjerg BJ, Court-Payen M, et al. Are bone erosions detected by magnetic resonance imaging and ultrasonography true erosions? A comparison with computed tomography in rheumatoid arthritis metacarpophalangeal joints. *Arthritis Res Ther.* 2006;8:R110.
15. Backhaus M. Sonography. In: Hochberg MC, Silman AJ, Smolen JS et al, eds. *Rheumatoid Arthritis*. 1st edn. Philadelphia: Mosby;2009:267-274.
16. Wakefield RJ, Balint P, Szkudlarek M, et al; for the OMERACT 7 Special Interest Group. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol.* 2005;32:2485-2487.
17. Freeston JE, Conaghan PG. Outcome measurement in rheumatoid arthritis: magnetic resonance imaging. In: Hochberg MC, Silman AJ, Smolen JS, et al, eds. *Rheumatoid Arthritis*, 1st edn. Philadelphia: Mosby; 2009:275-278.
18. Fleming A, Crown JM, Corbett M. Early rheumatoid disease. I. Onset. *Ann Rheum Dis.* 1976;35:357-360.
19. Burra G, Katchis SD. Rheumatoid arthritis of the forefoot. *Rheum Dis Clin North Am.* 1998;24:173-180.
20. Gray RG, Gottlieb NL. Hand flexor tenosynovitis in rheumatoid arthritis. Prevalence, distribution, and associated rheumatic features. *Arthritis Rheum.* 1977;20:1003-1008.
21. Stone JH, Dena R. Episcleritis. www.uptodate.com/contents/episcleritis. Accessed March 6, 2015.
22. Rawlins B, Girardi FP, Boachie-Adjei O. Rheumatoid arthritis of the cervical spine. *Rheum Dis Clin North Am.* 1998;24:55-65.
23. Chellapandian D, Panchapekesa CR, Rukmangatha S, et al. The cervical spine involvement in rheumatoid arthritis and its correlation with disease severity. *J Indian Rheumatol Assoc.* 2004;12:2-5.

5 Remission and rheumatoid arthritis

Benazir Saleem

Introduction

Remission in rheumatoid arthritis (RA) is complex and multifactorial. The last 30 years have seen an exponential increase in the volume of publications relating to remission in RA (Figure 5.1) resulting in a greater understanding of the remission state, yet many questions remain unanswered [1]. There are many factors that need to be considered when discussing remission. Importantly, how is remission achieved? There is abundant evidence for early diagnosis and treatment alongside a treat to target approach; this is covered in detail in Chapter 3. After achieving remission, how is this state optimally defined? An overview of available and potential methods of defining remission will be presented in the first section of this chapter. The remission state should equate to stability of clinical disease (ie, the absence of flare) with no deterioration in function or radiographic deformity. The potential additional value of including imaging (ultrasound [US]/magnetic resonance imaging [MRI]) and immunological assessments (eg, cytokine and T cell subtypes) when defining remission in patients treated with biological therapies and traditional disease-modifying antirheumatic drugs (DMARDs) will be discussed.

The second section will focus on drug-free remission. Local and national guidelines suggest that after remission is achieved, gradual reduction of DMARDs and biological therapy should be initiated [2]. ‘Drug holidays’ are potentially beneficial to the patient and to the health service. For patients, gradual dose reduction after achieving remission will prevent over-treatment and allow the lowest effective dose to be determined. However,

in order to achieve this goal, patients are put at risk of disease flare and subsequent loss of remission and adverse long-term outcomes. There is evidence that patients with established RA in remission treated with DMARDs are likely to flare when monotherapy is withdrawn [3]. However, sustained drug-free remission is possible after early aggressive therapy with combination methotrexate (MTX) and tumor necrosis factor (TNF)-blocking therapy [3]. This section will also present illustrations highlighting rates and predictors of successful drug cessation.

Defining remission

Achieving remission is associated with improved function and reduced radiographic progression (Figure 5.2) [4]. The most commonly used definitions of remission are presented in Table 5.1.

The 1981 American College of Rheumatology remission criteria

The American College of Rheumatology (ACR) remission criteria [5] for RA were proposed by a committee in 1981 but have since been criticized for being too stringent. For example, it has been shown that most healthy people over 50 in Finland do not meet ACR criteria for remission [6]. Overall, more realistic criteria was necessary for accurately reporting outcomes in clinical trials.

Disease activity score

The disease activity score (DAS) was developed to assess disease activity in early RA [7]. The original DAS includes four variables: Ritchie articular index (RAI) of tender joints [8], a 44-swollen joint count (SJC), erythrocyte sedimentation ration (ESR), and global health visual analogue scale (VAS) [7]. This was modified to a DAS28 that includes an account of 28 tender and swollen joints [9]. A DAS28 <2.6 and DAS <1.6 corresponded to ACR remission criteria. However, these composite indices have been validated against the modified ACR remission criteria, and patients may fulfill criteria for remission yet have ongoing tender and swollen joints.

The simplified disease activity index

The simplified disease activity index (SDAI) score is a continuous numerical index of disease activity validated in RA [10]. The index ranges from 0.1 to 86. The clinical disease activity index (CDAI) omits C-reactive protein (CRP) levels and ranges from 0–76. It is the only composite index to measure remission that does not include a laboratory measure and hence

can be calculated immediately. The cut-off for remission for SDAI and CDAI is <3.3 and <2.8 respectively, which allows for less disease activity than DAS28 <2.6 ; hence, the SDAI has been described as a more accurate measure of remission as it allows for less residual disease [11].

American College of Rheumatology/European League Against Rheumatism 2011 remission criteria

The need for new remission criteria was based on the problems with the old criteria. The American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) committee members, who began work in 2007, had decided that a truly useful definition of remission would reflect ‘absence of disease activity’ and would represent a state, rather than a transition between states [12]. The chosen criteria should predict absence of X-ray damage progression, good functional outcomes, future remission, and minimal disease activity (ie, show stability) (Table 5.2). Two criteria for defining remission were determined:

- the SDAI, as fulfillment of this remission criteria was associated with a positive likelihood ratio of 4.77 for radiographic and functional stability; or
- scores for the following measures are all ≤ 1 : tender joint count, swollen joint count, CRP (mg/dL), and patient global assessment (0–10 scale; positive likelihood ratio for radiographic and functional stability is 7.18).

There are potential weaknesses to these criteria and it should be remembered that the criteria are ‘preliminary’ and therefore subject to modification. The sensitivities and likelihood ratios for predicting a very good outcome in terms of X-rays and function were relatively modest for all evaluated sets of criteria. For example, the proportion of patients with good outcomes on X-ray using the two proposed criteria sets were 77%, meaning that a substantial proportion (23%) still progress radiographically [12]. Also, the criteria were based on datasets from clinical trials, which provide complete and long-term follow-up data for a large number of patients, but only include selected subgroups of patients. The criteria do not include imaging assessments.

An observational cohort has confirmed rates of continued radiographic progression of 20% in patients fulfilling ACR/EULAR 2011 remission criteria but, interestingly, similar rates were also observed for the other remission criteria: 24% of patients in SDAI remission, 19% in CDAI remission, and 30% in DAS28–CRP remission [13]. There were no significant differences between the groups in disease duration, antibody status, or treatment. The positive likelihood ratio for good radiographic outcome was 2.6 for ACR/EULAR criteria, 2.1 for SDAI, 2.8 for CDAI, and 1.5 for DAS28–CRP (Figure 5.3) [13].

Active foot or ankle synovitis

There has also been much debate with regards to the use of the 28-joint-count assessment required to calculate the DAS28 and SDAI. A DAS28 < 2.6 allows for a considerable number of tender and swollen joints and it has been suggested that it will misclassify 13/100 patients in remission [14]. Also, the DAS28 does not include assessment of feet and ankles, which has caused some debate [14–17]. Wechalekar et al have identified that significant proportions of patients with early RA treated with DMARDs fulfilling the validated remission criteria have ongoing foot synovitis (Table 5.3) [18]. However, data presented by the ACR/EULAR committee suggest that the impact of misclassification on long-term outcome is small.

Imaging remission

The use of sensitive imaging modalities (MRI/US) have allowed direct visualization of the synovium and have been validated to assess structural damage and inflammation. US can be used to assess two aspects of synovitis: its morphology and quantity using grayscale (GS) and synovial vascularity as measured by color or power Doppler (PD). It is the latter component that has attracted particular attention as this has been shown to better correlate with the activity of the inflammatory process than GS alone [19,20]. MRI bone edema (osteitis) is considered to be the best predictor of future joint damage [21].

Ultrasound has been used in studies to assess remission patients and a summary of the key papers relating to US and remission is given in Table 5.4 [3,22–28]. To date, there is no validated definition of US-defined imaging remission with studies using both stringent (ie, the complete absence of PD and GS) and less stringent definitions. The majority of US scoring methods are based on a semi-quantitative scale from 0–3 where 0=none, 1=mild, 2=moderate, and 3=severe [29]. The total score for each patient was calculated by summing the corresponding scores for each joint region. Questions remain as to whether aiming for imaging remission is achievable, how it should be defined, and whether it is treatable. There are a number of considerations: for example, the number of joints to be scanned, which scoring systems should be used (and what cut-offs), and likelihood of concurrent osteoarthritis. The studies described in Table 5.4 have used between 5 and 42 joints. For US to be a practical and feasible imaging modality, identifying the minimal number of joints scanned that still provide the maximum amount of clinically and patient-relevant information is crucial. This section of the chapter will present evidence for the presence of imaging-detected synovitis and the clinical significance where

data are available. There is a drive to include imaging assessments in remission criteria but as discussed, there are many unanswered questions.

Detection of imaging-detected inflammation

In patients treated with DMARDs, discrepancies have been documented between clinical findings and long-term outcomes [30,31]. Some have explained this phenomenon as dissociation between synovitis and erosive damage [32] but it could be that clinical measures of disease activity are insensitive to detect synovitis especially in low disease-activity states.

Brown et al confirmed that patients in remission, as defined by the treating rheumatologist, continue to progress radiographically, as illustrated in Figure 5.4, which shows the cumulative probability distribution of the percentages of symptomatic and asymptomatic patients with a given change in total radiographic (X-ray score [smallest detectable change {SDC}]) [22]. A statistically significant 19% of the total cohort had worsening of total X-ray score that exceeded the SDC; 11% and 12% of patients who fulfilled ACR or DAS28 remission criteria, respectively, had radiographic progression by 12 months. The same cohort underwent detailed clinical and imaging assessments at baseline. In this cohort of remission patients with established RA (median 7 years), about 50% of the patients had increased PD activity and bone marrow edema (Figure 5.5; Table 5.5). Similar results have been described in other studies [25–27], but with evidence that patients with early RA in remission on DMARDs have less imaging synovitis when compared to patients with long-standing disease. Of particular importance, the PD score for the dominant hand metacarpophalangeal (MCP) joints was also significantly associated with radiographic progression anywhere in the hands and feet ($P=0.0036$). Furthermore, in patients with no painful, tender, or swollen joints, 16% experienced radiographic progression that was predicted by baseline PD activity. At 12 months, 11% of patients who satisfied ACR remission criteria and 12% of patients who satisfied DAS28 remission criteria progressed radiographically. Looking at progression in individual joints, no clinical findings at baseline were significantly associated with an increased likelihood of progression. However, a positive PD signal (odd ratio [OR]=12.21; $P<0.001$), the scores for the PD (OR=4.00; $P<0.001$), synovial hypertrophy (OR=2.31; $P=0.0032$), and MRI synovitis (OR=2.98; $P=0.002$) were associated with significantly higher odds of progression (Table 5.6).

MRI studies involving patients in remission have used cohorts that have included patients treated with DMARDs and biologics. MRI characteristics of patients in remission (99% on DMARDs, 15% on biologics) was published recently [34]. This study evaluated 294 patients

in DAS28 remission and low-disease activity (LDA). MRI of the unilateral wrist and/or MCP joints 2–5 were acquired and synovitis, erosions, and osteitis were defined and scored according to the Outcome MEasures in RA Clinical Trials RA MRI Scoring system (OMERACT RAMRIS) [35]. Osteitis (bone edema) is a known independent predictor of subsequent bone erosions [36]. MRI inflammation was detected in the majority of patients, with synovitis and osteitis in wrist and/or MCP joints in 95% and 35% of patients, respectively (Figure 5.6) [34]. Furthermore, MRI-detected osteitis and bone erosion scores were significantly lower in patients with early RA (<1 year) in remission compared to those with established RA (>1 year), but there was no difference in synovitis scores (Figure 5.7) [34]. Also, in a population of patients in DAS28 remission or LDA (83.5% on DMARDs, 13% on biologics, and 44.7% on oral prednisolone), MRI-detected synovitis and bone marrow edema (BME) were present at baseline [20]. BME was a predictive factor of MRI-determined structural progression in patients with RA in clinical remission or with LDA [20].

Imaging-detected synovitis predicts flare of disease in patients in DMARD-induced clinical remission

US-determined PD activity predicts disease flare in patients in DMARD-induced clinical remission. 35% of patients with increased PD at baseline had a flare, compared with 11% of those with no PD activity (OR=4.08 [1.26–13.19]; $P=0.014$), giving a sensitivity of 83% (95% confidence interval [CI]; 62–95%), specificity of 45% (33–57%), positive predictive value of 35% (23–48%), and negative predictive value of 89% (72–96%) [37]. There was also evidence that the number of joints scoring >0 for PD at baseline was associated with subsequent flare (OR=1.43 [1.01–2.02]; $P=0.044$) [37]. There were no substantive associations with the presence of GS synovial hypertrophy or the number of joints showing GS synovial hypertrophy at baseline. Although of importance to those without access to US, flare was also associated with poor baseline function and quality of life (QoL) measures: Health Assessment Questionnaire Disability Index (HAQ-DI; OR per 0.1 unit=1.27 [1.07–1.52]; $P=0.006$) and RAQoL (OR=1.10 [1.01–1.20]; $P=0.036$) (Figure 5.8).

Role of imaging in patients in TNF blocker-induced clinical remission

Unlike the data for patients in DMARD-induced clinical remission, there is overwhelming evidence that treatment with TNF-blocker therapy or other biologics is associated with superior radiographic outcomes when compared to MTX monotherapy (Figure 5.9) [38].

Studies have confirmed the presence of US-detected imaging synovitis in patients treated with TNF-blocker therapy but data regarding the long term clinical, functional, and radiographic impact are scarce [38]. Furthermore, it had been postulated that patients in remission treated with TNF-blocking therapy would have less imaging-detected synovitis when compared to patients in remission treated with DMARDs [24].

The joints of matched patients with disease in remission induced either by the combination of TNF blockade and MTX or by DMARD therapy were imaged for US synovitis [24]. Complete remission according to imaging results (using a GS synovitis score of 0 and a PD activity score of 0) was seen in 10% of patients in the combination treatment group compared with 16% of patients in the DMARD group (P =not significant). However, while more patients in the combination treatment group than in the DMARD group had a power Doppler activity score of 0 (52% versus 40%; $P=0.229$), significantly more patients in the combination treatment group had a GS synovitis score ≥ 2 ($P<0.001$) [24]. There were, however, differences in disease duration and duration of remission between the groups (Figure 5.10).

Thus, data have been presented in this chapter that confirms the usefulness of imaging assessments in patients in clinical remission. Patients can fulfill clinical criteria for remission, yet still have evidence of synovitis detectable both clinically and by ultrasound, and this has been shown to produce structural damage and predict flare. The failure of clinical examination to correlate with PD activity and GS synovial hypertrophy may be due to the fact that clinical scores are not stringent enough (ie, a patient may fulfill the current definitions of remission yet have clinical evidence of ongoing disease activity [eg, tender or swollen joints]). However, classifying patients using more stringent remission criteria resulted in reduced signs and symptoms of inflammation, but the percentage of joints with PD activity was not reduced, even in those without signs or symptoms (Figures 5.11 and 5.12) [28].

Immune-mediated remission

For a patient to be in complete remission, there should be the absence of clinical signs and symptoms of the disease (no tender or swollen joints plus normal inflammatory markers), minimal evidence of imaging-detected synovitis, and normalization of the immune system. Evidence has emerged that T cell subsets can be used to improve the remission assessment and have clinical prognostic importance. Of relevance to this chapter, data have been published suggesting that achieving normalization of the immune system, as determined by levels of naïve cells, T regulatory cells, and other abnormally differentiated T cells, is associated with

sustained clinical remission after stopping TNF blocker therapy (Table 5.7) [3]. Further work in this area is required.

A multi-biomarker disease activity (MBDA) blood test has recently been validated. The MBDA test employs an algorithm to combine the levels of 12 serum biomarkers in a pre-specified algorithm into a single score from 1 to 100 to provide an objective measure of RA disease activity [39]. A score of ≤ 25 indicates remission, whereas scores falling into the ranges 26–29, 30–44, and >44 indicate low, moderate, and high RA disease activity, respectively. A high MBDA score is associated with radiographic progression in patients in DAS28 remission (Figure 5.13) [39].

Drug-free remission

EULAR has published 15 recommendations for the management of RA [2]. Amongst these, it is recommended that if a patient is in remission, after having tapered steroids, one can consider tapering biological DMARDs, especially if this treatment is combined with a synthetic DMARD [2]. In cases of sustained long-term remission, cautious titration of synthetic DMARD dose can be considered, as a shared decision between patient and doctor. Data exist for drug-free and biologic-free remission and will be discussed.

DMARD-free remission

Established rheumatoid arthritis

The quest for drug-free remission for patients with RA is longstanding. It was especially significant when therapeutic options were limited by significant toxicity and poor patient compliance. Several small randomized controlled trials published in the 1970s and 1980s suggested that long-term maintenance therapy with DMARDs was effective in preventing flares of disease [40–43]. A 52-week randomized, double-blind, placebo-controlled, multi-center study was conducted to assess the effect of stopping DMARD therapy in 285 patients with RA [44]. The main study endpoint was flare of disease, as defined by recurrence of clinical synovitis at which point protocol medication (DMARD/placebo) was discontinued and therapy with original DMARD was recommenced (Figure 5.14) [45]. Disease flares occurred in 53 patients from the placebo group and in 30 patients from the continued treatment group. The cumulative incidence of flare after 52 weeks was 38% for placebo and 22% for continued treatment ($P=0.002$) [45].

Early rheumatoid arthritis

It would be expected that the advent of treat to target approaches to patients with RA and early treatment would convey an additional advantage and create a remission state that was sustainable even after cessation of drug-free therapy. Van der woude et al investigated the prevalence of and prognostic factors for sustained DMARD-free remission in two large, independent inception cohorts (Leiden Early Arthritis Clinic and from the British Early Rheumatoid Arthritis Study) of RA patients treated with conventional therapy) (Figure 5.15) [46]. A very stringent definition of remission was used in the study: the sustained absence of synovitis for at least 1 year after the discontinuation of therapy with DMARDs. Sustained DMARD-free remission was achieved by 9.4–15% of patients. Clinical predictors of drug-free remission included acute onset, short symptom duration before inclusion, not smoking, little radiographic damage at baseline, absence of IgM rheumatoid factor (IgM-RF), and absence of HLA shared epitope alleles. Multivariate analyses revealed symptom duration and the absence of autoantibodies (anti-cyclic citrullinated peptide 2 and IgM-RF) as independent predictors.

The BeSt study has provided further evidence for drug-free remission [47]. In this multi-centre, randomized clinical trial, 508 patients were recruited and allocated to one of four treatment strategies: group 1: sequential monotherapy; group 2: step-up combination therapy; group 3: initial combination with tapered high-dose prednisolone; group 4: initial combination therapy with infliximab. The goal of each treatment arm was to reach and sustain a DAS44 ≤ 2.4 , indicating low disease activity. If patients maintained a DAS44 < 2.4 for at least 6 months, treatment was decreased gradually and subsequently stopped [47]. During the study period, 64% of patients achieved a DAS < 2.4 for at least 6 months and therapy with infliximab was discontinued. Of these patients, 52 were in clinical remission (DAS < 1.6) when therapy was stopped and 56% were able to permanently discontinue infliximab during the 2-year follow-up period [47]. Additionally, of the 77 who discontinued treatment, 10 patients (13%) flared after discontinuing infliximab for a median of 3.7 months and 8 regained previous levels of disease control after reintroduction of infliximab (DAS ≤ 2.4) [47].

The 5-year analysis of the 508 patients showed that drug-free remission could be achieved with no significant differences between the four groups (Table 5.8). During 5 years of DAS-steered treatment, nearly 25% of patients with RA achieved drug-free remission and 46% restarted DMARD monotherapy because of a relapse, the majority of whom again achieved

clinical remission within 3–6 months without showing radiological progression during the relapse (Figure 5.16) [46,48].

Biologic-free remission

The question of when and for whom TNF-blocker therapy be stopped was addressed by Saleem et al [3]. Of the 47 patients in DAS28 remission who stopped TNF-blocker therapy, 40% sustained remission [3]. Sustained remission was associated with shorter duration of disease (18 versus 72 months; $P<0.0001$), lower HAQ scores (0 versus 0.5; $P=0.012$), and lower RAQoL scores (0 versus 3.0; $P=0.039$) but no difference in duration of remission (10 versus 12 months; $P=0.31$) when compared to patients that flared (Table 5.9). Significantly more patients in the late treatment group flared (17/20 versus 11/27) than in the early disease group ($P<0.001$), with only 3 patients (15%) in this group able to sustain remission after withdrawal of therapy. Flare of disease in this group occurred a median of 4 weeks (interquartile range [IQR]: 2–10 weeks) after stopping therapy, in contrast to much later in the early treatment group (median: 14 months; IQR: 9–24 months).

Optimal dose reduction regimes for patients in remission

Sustained drug-free remission is uncommon and biologic-free remission is more likely if combination TNF-blocker and MTX is used as first-line therapy [3]. There are, however, no guidelines regarding the optimal method of dose reduction. Smolen et al have provided evidence that dose reduction of etanercept is effective in maintaining a remission state [49]. Patients with moderate disease activity (DAS28 >3.2 and <5.1) despite MTX therapy were recruited into the initial open-label phase of the study and received etanercept and MTX for 36 weeks. At this point, if the patient achieved sustained LDA, they were randomly assigned (1:1:1) to one of three treatment groups: 50mg etanercept plus methotrexate, 25mg etanercept plus methotrexate, or placebo plus methotrexate. Patients were stratified in blocks of three by DAS28 response (eg, LDA or remission) at week 36. The primary endpoint was the proportion of patients with low disease activity at week 88 in the groups given 50 mg etanercept or placebo in the double-blind period. Whilst these results are very promising (Figure 5.16), for patients in the UK, TNF-blocker therapy is not available unless patients fulfill a DAS28 >5.1 on two occasions at least 4 weeks apart after failing at least two DMARDs. However, these data do provide a compelling argument for treatment with TNF-blocker therapy in patients with moderate disease activity.

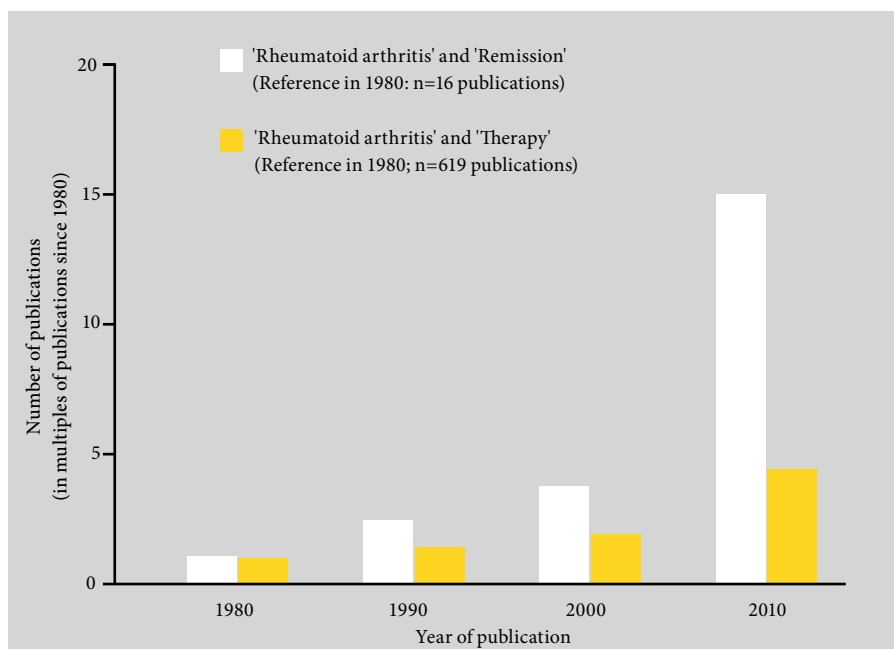


Figure 5.1 An exponential rise in the number of publications relating to remission. The graph shows the disproportional increase of studies on remission of rheumatoid arthritis (white bars) when compared to studies of treatment of rheumatoid arthritis (yellow bars) over the years. Reproduced with permission from Aletaha [1]©BMC.

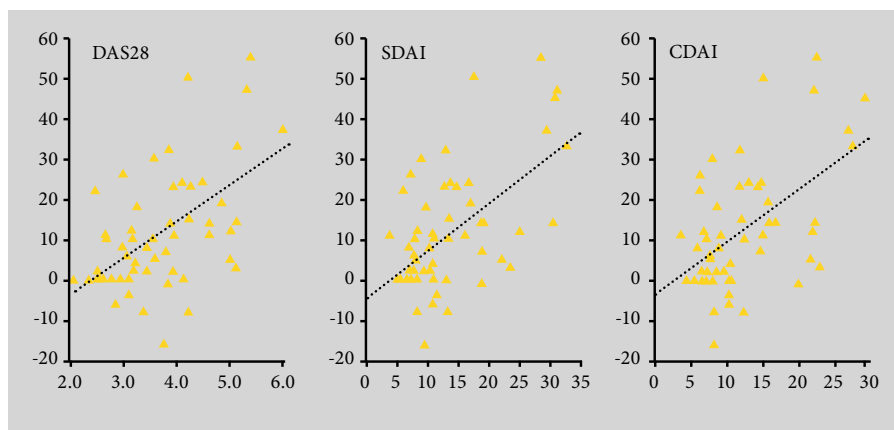


Figure 5.2 Levels of rheumatoid arthritis disease activity measures are associated with X-ray progression. Correlation with changes in Larson score over 3 years. CDAI, Clinical Disease Activity Index; DAS28, 28-joint Disease Activity Score; SDAI, Simplified Disease Activity Index. Reproduced with permission from Aletaha et al [4]©BMJ.

Definition	Calculation/definition	Remission criteria
DAS28	$0.56 \cdot \sqrt{(\text{TJC28})} + 0.28 \cdot \sqrt{(\text{SJC28})} + 0.36 \cdot \ln(\text{CRP} + 1) + 0.014 \cdot \text{GH} + 0.96$	<2.6
SDAI	TJC28 + SJC28 + CRP + PTglobal + PHYglobal	≤3.3
CDAI	TJC28 + SJC28 + PTglobal + PHYglobal	≤2.8
ACR (1981)	Early morning stiffness (<15 minutes) No fatigue No joint pain on history No joint tenderness or pain on motion No soft tissue swelling in joints or tendon sheaths Normal inflammatory markers	5 or more, for 2 consecutive months
ACR/EULAR 2011 (Boolean)	TJC28* & SJC28* & CRP & PTglobal	All ≤1

Table 5.1 Clinical definitions of remission. ACR, American College of Rheumatology; CDAI, clinical disease activity index; CRP, C-reactive protein (mg/L for 28-joint disease activity score [DAS28]–CRP; mg/dL for other definitions); GH, general health (on a 0–100 mm Visual Analogue Scale [VAS]); PHYglobal, physician's global assessment on a 0–10 cm VAS; PTglobal, patient's global assessment on a 0–10 cm VAS; SDAI, simplified disease activity index; SJC28, 28 swollen-joint count; TJC28, 28 tender-joint count.

	% in remission with good outcome	% NOT in remission with good outcome	Positive likelihood ratio	P-value
TJC28, SJC28, CRP ≤1	46%	17%	3.2	<.0001
+ PtGA ≤1	66%	17%	7.2	<.0001
+ Pain ≤1	60%	17%	5.7	<.0001
+ PhGA and PtGA ≤1	68%	17%	8.0	<.0001
+ PhGA and Pain ≤1	64%	18%	6.7	<.0001
+ PtGA and Pain ≤1	64%	17%	6.8	<.0001
+ PhGA, PtGA and Pain ≤1	67%	18%	7.5	<.0001

Table 5.2 Predictive validity of the proposed remission definitions for good outcome in radiographic damage and functional outcome. Good radiographic outcome was defined as a change of ≤0 in Sharp/van der Heijde scores between 12 and 24 months after baseline; good outcome on the Health Assessment Questionnaire (HAQ) was defined as a change of ≤0 and a score of ≤0.5 at both the 12-month and 24-month time points. CDAI, clinical disease activity index; CRP, C-reactive protein; DAS28, 28-joint disease activity score; PhGA, physician/observer global assessment; PtGA, patient global assessment; SDAI, simplified disease activity index; SJC, swollen joint count; TJC, tender joint count. Adapted with permission from Felson et al [12] ©BMJ.

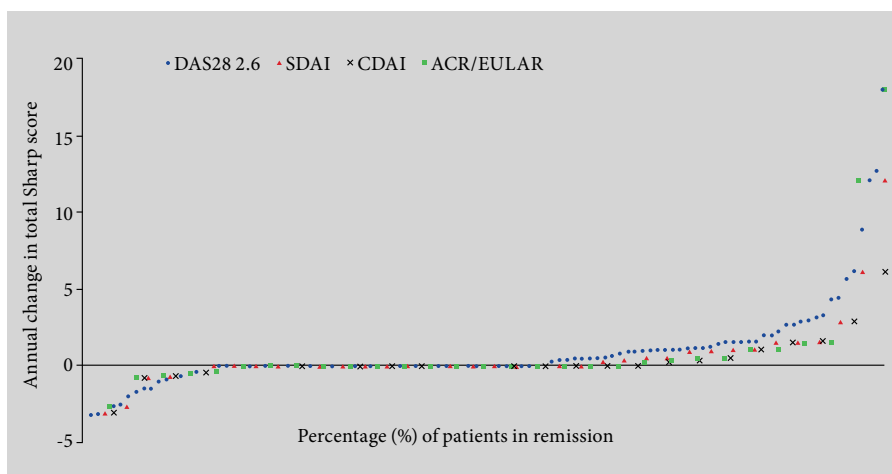


Figure 5.3 Cumulative probability plot for patients in remission according to DAS28-CRP, SDAI, CDAI and ACR/EULAR criteria at baseline. Each dot represents the annual change in TSS (y-axis) for an individual patient. ACR, American College of Rheumatology; CDAI, clinical disease activity index; DAS28-CRP, 28-joint disease activity and C-reactive protein score; EULAR, European League Against Rheumatism; SDAI, simplified disease activity index; TSS, van der Heijde-modified Sharp score. Reproduced with permission from Lillegraven et al [13] ©BMJ.

Remission criteria	Percentage of patients with foot synovitis (%)
DAS28-ESR <2.6	43
CDAI ≤2.8*	28
SDAI ≤3.3*	27
2011 ACR/EULAR* (Boolean criteria)	22

Table 5.3 Presence of foot synovitis in patients meeting remission criteria at 6 months after starting disease-modifying antirheumatic drugs. ACR, American College of Rheumatology; CDAI, clinical disease activity index; DAS28-ESR, 28-joint disease activity using erythrocyte sedimentation rate score; EULAR, European League Against Rheumatism. *28-joint-count. Adapted with permission from Wechalekar et al [18] ©Wiley.

Author	Year	Number of patients (n)	Treatment(s)	Definition of clinical remission for inclusion into study
Brown et al [22]	2006	107, late (dd median 7 years; 2–38 years)	DMARD	As defined by treating rheumatologist
Wakefield et al [23]	2007	10, early (dd median 6 months; 3–11 months)	Anti-TNF	DAS28 <2.6 NB: Patients had active disease at inclusion
Saleem et al [24]	2009	100, late (dd median 120 months; 72–183 months)	50 DMARD, 50 Anti-TNF	DAS28<2.6
Balsa et al [25]	2009	97, late (dd mean 5.9 years)	DMARD, biologic	As defined by treating rheumatologist
Scire et al [26]	2009	106, early	DMARD	DAS<1.6
Peluso et al [27]	2011	94 (48 early: 6.9 months +/- 3; 46 late: 118.9 months +/- 71.7)	Early: DMARD +/- Anti-TNF Late: All DMARD +/- Anti-TNF	DAS<1.6
Saleem et al [28]	2010	47 (27 early: dd 19 months; 20 late: dd 120 months)	All DMARD and Anti-TNF	DAS28<2.6
Saleem et al [29]	2011	128, late; (dd 8 years; 5–13 years)	DMARD and TNF blocker	DAS28<2.6

Table 5.4 Summary of key papers relating to ultrasound and remission in rheumatoid arthritis. ACJ, acromioclavicular joint; dd, differential diagnosis; DAS28, 28-joint disease activity score; DMARD, disease-modifying antirheumatic drug; GS, grayscale; MCPJ, metacarpophalangeal joint; MTP, metatarsophalangeal; PD, power Doppler; PIPJ, proximal interphalangeal joint; SH, synovial hypertrophy; SCJ, sternoclavicular; TNF, tumor necrosis factor. Data taken from [22–29].

Joints scanned	Definition of ‘imaging remission’	Time to scan (minutes)
5 joints: dominant wrist and MCPJ2–5	Used a semi-quantitative score Did not define imaging remission	30
42 joints: shoulders, elbows, wrists, MCPJ, PIPJ, knees, ankles, MTPJ	Semi-quantitative score for GS and PD Remission defined as absence of GS and PD	50
5 joints: dominant wrist and MCPJ2–5	Semi-quantitative score for GS and PD Remission defined as absence of GS and PD	30
42 joints: shoulders, elbows, wrists, MCPJ, PIPJ, knees, ankles, TNJ and MTPJ	Semi-quantitative for GS and PD Remission defined as an absence of joints with a PD signal	45 (including documentation)
44 joints: Shoulders, elbows, wrists, MCPJ, PIPJ, SCJ, ACJ, knee, ankle, MTP	Semi-quantitative score for PD and GS; did not define imaging remission; calculated a summative score	60
10 joints (12 joint areas): bilateral MCPJ 2–3, PIPJ 2–3, wrist (2 regions)	Used 3 definitions: active synovitis (SH and PD), US remission: no SH or PD Inactive synovitis: SH but no PD	Not documented
5 joints: dominant wrist and MCPJ2–5	Semi-quantitative score for GS and PD Remission defined as absence of GS and PD	30
5 joints: dominant wrist and MCPJ2–5	Semi-quantitative score Imaging remission: 1. no GS or PD; 2. low disease activity (GS $\leq$ 1) and PD=0 3. PD=0 4. PD $\leq$ 1	30

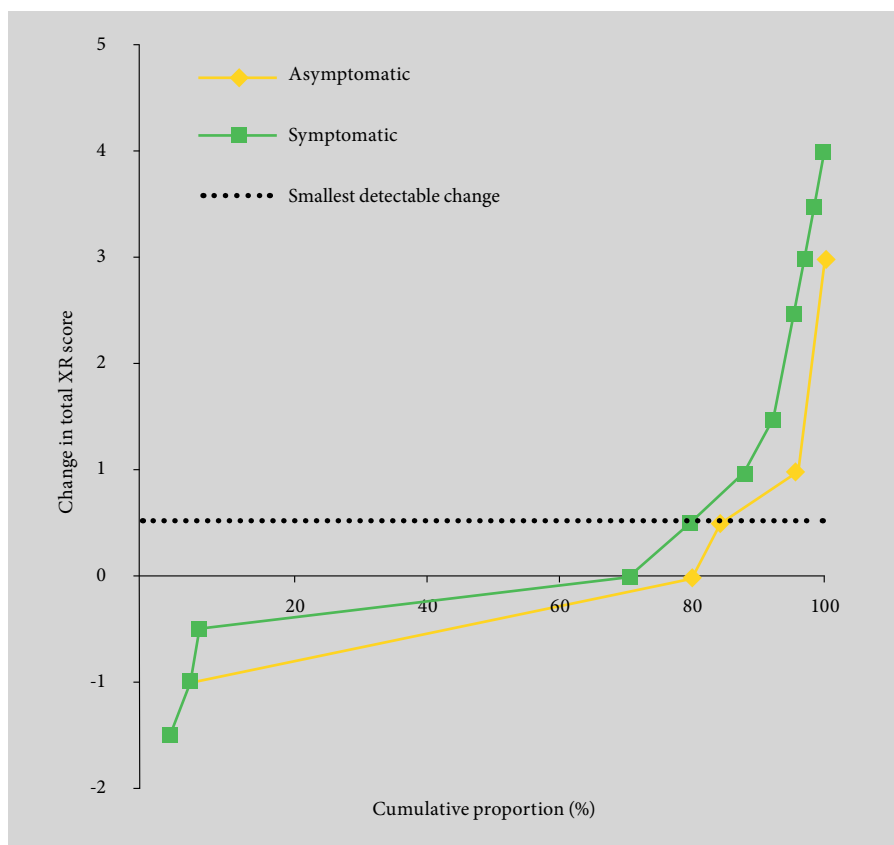


Figure 5.4 Cumulative probability distribution of the percentages of symptomatic and asymptomatic patients with a given change in total radiographic X-ray score. XR, X-ray radiography. Reproduced from Brown et al [33]©Wiley.

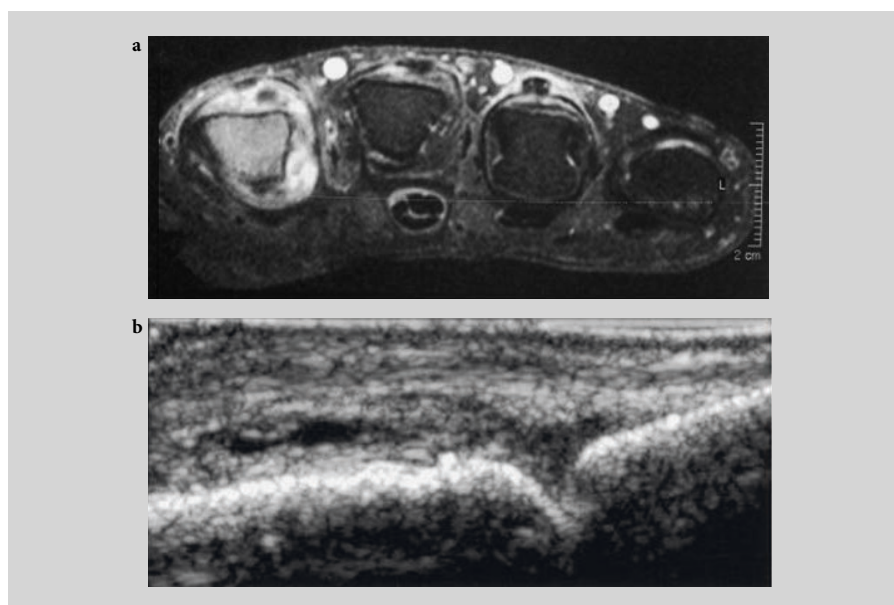


Figure 5.5 Imaging detected synovitis in patients with RA in clinical remission. Axial section of a T1 spectral presaturation with inversion recovery, postgadolinium magnetic resonance imaging scan of the metacarpophalangeal (MCP) joints of the right hand of a patient with rheumatoid arthritis in clinical remission, demonstrating synovitis in the second MCP joint, flexor tenosynovitis of the third flexor tendon, and extensor tenosynovitis of the third and fourth extensor tendons (a). Longitudinal section of an ultrasonography scan of the second MCP joint of the right hand of a patient with RA in clinical remission, demonstrating grayscale changes of synovial hypertrophy (b). L, left.

Variable	DAS28 remission criteria	1981 ACR remission criteria
Ultrasound		
Patients with synovial hypertrophy no. (%):	48 (84.2)	47 (81.0)
Patients with increased power Doppler signal no. (%):	29 (50.9)	32 (55.5)
MRI		
Patients with synovitis, no (%):	51 (96.2)	49 (96.1)
Patients with bone marrow edema, no (%):	28 (51.9)	25 (47.2)

Table 5.5 Criteria for remission. American College of Rheumatology (ACR) criteria and 28-joint disease activity score (DAS28) scores compared with imaging measures of disease activity. Adapted with permission from Brown et al [33] ©Wiley.

Baseline variable	No radiographic progression (n=370)	Radiographic progression (n=10)	OR (95% CI)	P-value
Clinical findings, no. (%) of patients				
Painful joint count	12 (3)	1 (10)	3.32 (0.39, 28.30)	0.273
Tender joint count	18 (5)	1 (10)	2.17 (0.26, 18.10)	0.473
Swollen joint count	75 (20)	3 (30)	1.69 (0.43, 6.67)	0.457
Imaging findings				
US SH score, median (IQR)	1 (0–1)	1 (0–2)	2.31 (1.06, 5.52)	0.032
US PD score, median (IQR)	0 (0–0)	0.5 (0–2)	4.00 (1.98, 8.08)	<0.001
MRI synovitis score, median (IQR)	0 (0–1)	2.5 (0–3)	2.98 (1.49, 5.97)	0.002
MRI BME score, median (IQR)	0 (0–0)	0 (0–0)	2.26 (0.98, 5.22)	0.057
No. (%) US SH positive	203 (55)	7 (70)	1.92 (0.49, 7.54)	0.350
No. (%) US PD signal positive	28 (8)	5 (50)	12.21 (3.34, 44.73)	<0.001

Table 5.6 Associations between the clinical and imaging findings at baseline and radiographic progression in individual joints (dominant-hand metacarpophalangeal joints) over 12 months. BME, bone marrow edema; CI, confidence interval; IQR, interquartile range; MRI, magnetic resonance imaging; OR, odds ratio; PD, power Doppler; SH, synovial hypertrophy; US, ultrasound. Reproduced with permission from Brown et al [33] ©Wiley.

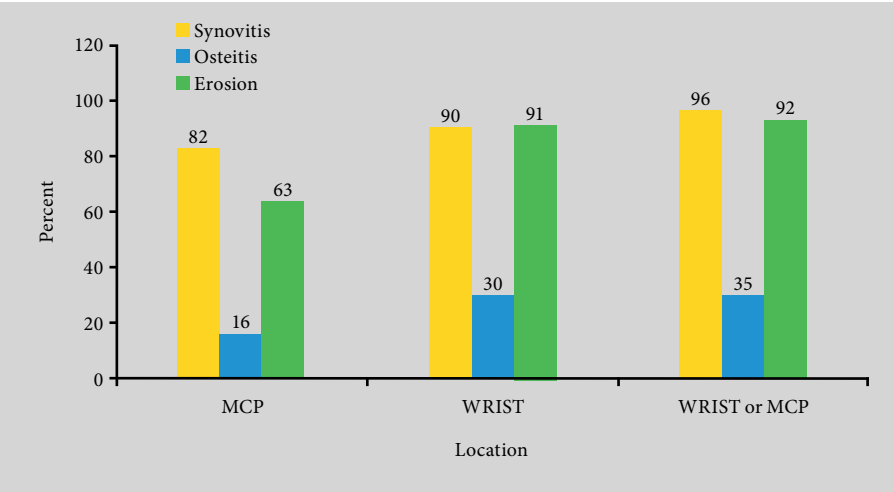


Figure 5.6 Frequencies of synovitis, osteitis, and erosions in patients with clinical remission. Remission defined as 28-joint disease activity score (DAS28) <2.6. MCP, metacarpophalangeal joint. Reproduced with permission from Gandjbakhch et al [34] ©The Journal of Rheumatology Publishing Company.

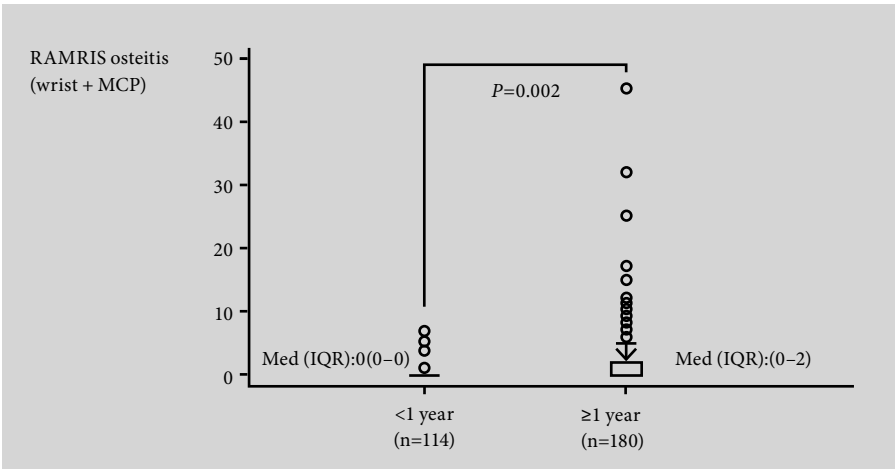


Figure 5.7 Magnetic resonance imaging osteitis in patients with early rheumatoid arthritis and late rheumatoid arthritis in clinical remission or low disease activity state. IQR, interquartile range; MCP, metacarpophalangeal joint; Med, median; RAMRIS, rheumatoid arthritis MRI scoring system. Reproduced with Gandjbakhch et al [34] ©The Journal of Rheumatology Publishing Company.

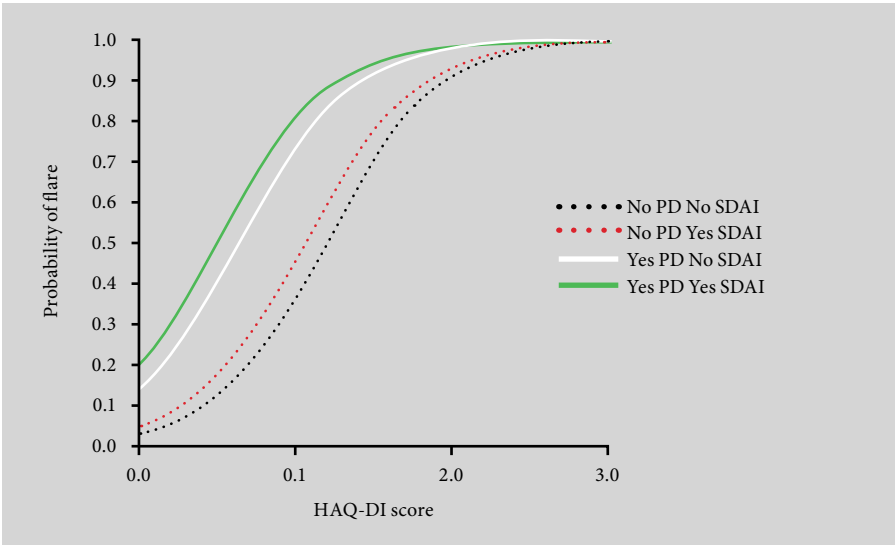


Figure 5.8 The probability of flare from the regression model that included power Doppler (PD), Health Assessment Questionnaire Disability Index (HAQ-DI) and Simplified Disease Activity Index (SDAI) remission. For all four lines, the probability of flare increases with increasing HAQ-DI score. The presence of PD (solid lines) gives an increased probability of flare compared with absence of PD (dotted lines), but the difference between being in SDAI remission (green and red lines) or not (white and black lines) is comparatively much smaller. Reproduced with permission from Saleem et al [37]©BMJ.

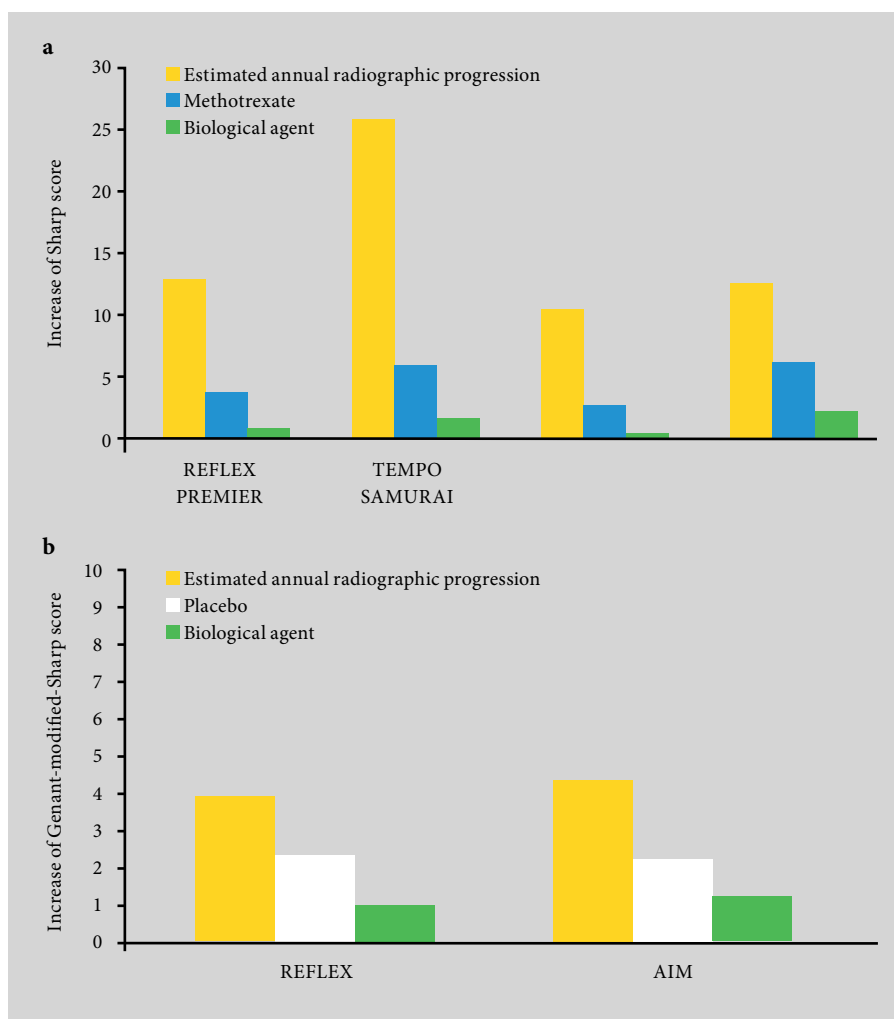


Figure 5.9 Estimated annual radiographic progression and change of joint damage on therapy. (a) Change in Sharp (or van der Heijde-modified Sharp) score during methotrexate monotherapy or with methotrexate and tumor necrosis factor (TNF) inhibitor (infliximab [ASPIRE], adalimumab [PREMIER], or etanercept [TEMPO]), or with various disease-modifying drugs (80% methotrexate at study start) compared with tocilizumab monotherapy (SAMURAI). Differences between treatment and methotrexate arms are significant ($P<0.001$ for all trials). (b) Change in Genant score in patients with inadequate response to methotrexate who continued this drug and received placebo, rituximab (plus methotrexate) (REFLEX), or abatacept (plus methotrexate) (AIM). Differences between treatment and placebo arms are significant: $P<0.005$ (rituximab); $P=0.012$ (abatacept). The estimated yearly progression rates were taken from the original reports of PREMIER and TEMPO and calculated from the respective means provided in the references for the other trials. Note the different scale when compared with (a). Reproduced with permission from Smolen et al [38] ©Lancet.

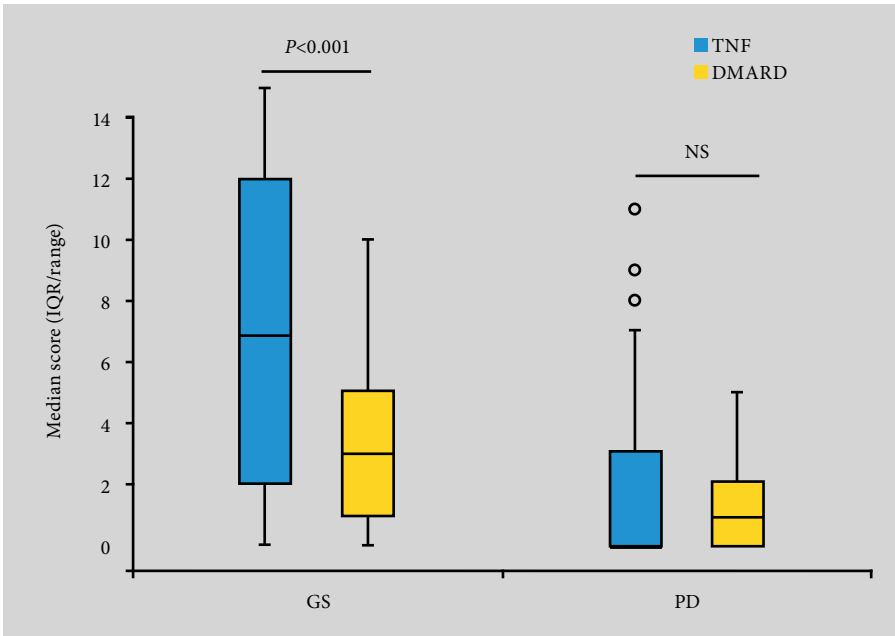


Figure 5.10 Patients in the combination tumor necrosis factor blocker group had more grayscale synovitis but no differences in power Doppler signal. DMARD, disease-modifying antirheumatic drug; GS, grayscale; IQR, interquartile range; PD, power Doppler; TNF, tumor necrosis factor. Reproduced with permission from Saleem et al [24] ©Wiley.

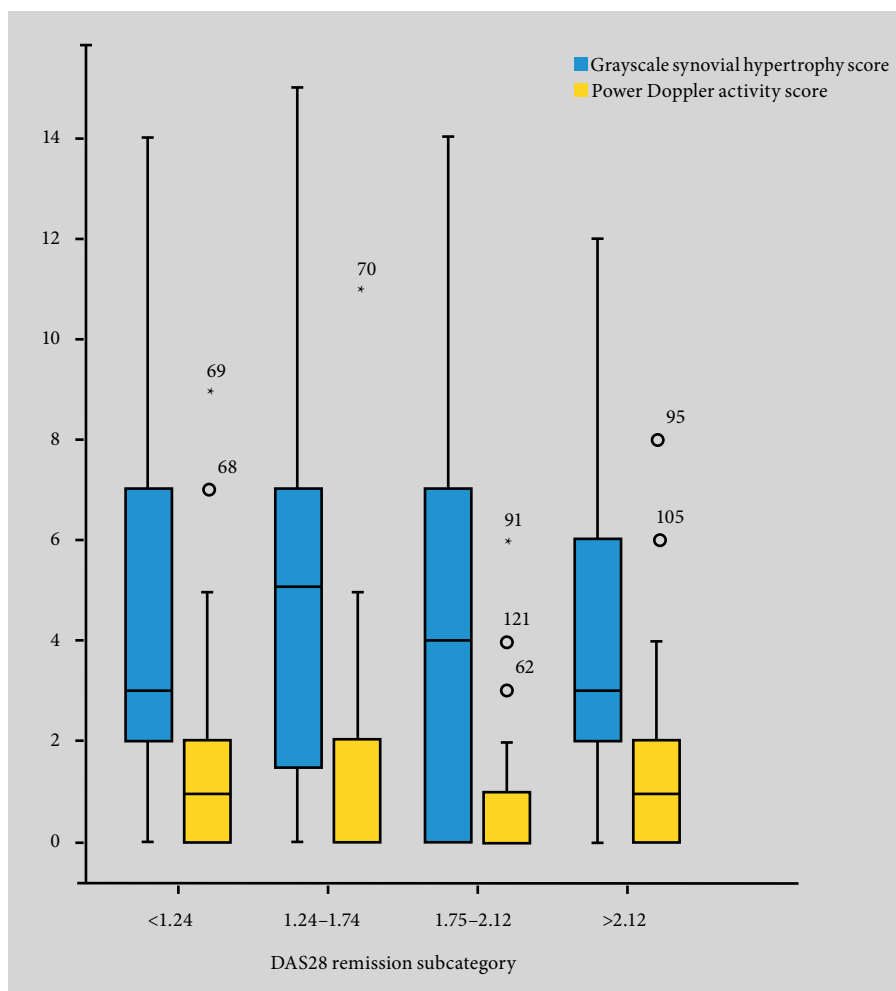


Figure 5.11 The relationship between stringent DAS28 subcategories of remission and total median power Doppler activity and total median grayscale synovial hypertrophy score per patients as detected by ultrasound. No significant difference was seen between the groups. DAS28, 28-joint disease activity score; GS, grayscale. Reproduced with permission from Saleem et al [28] ©BMJ.

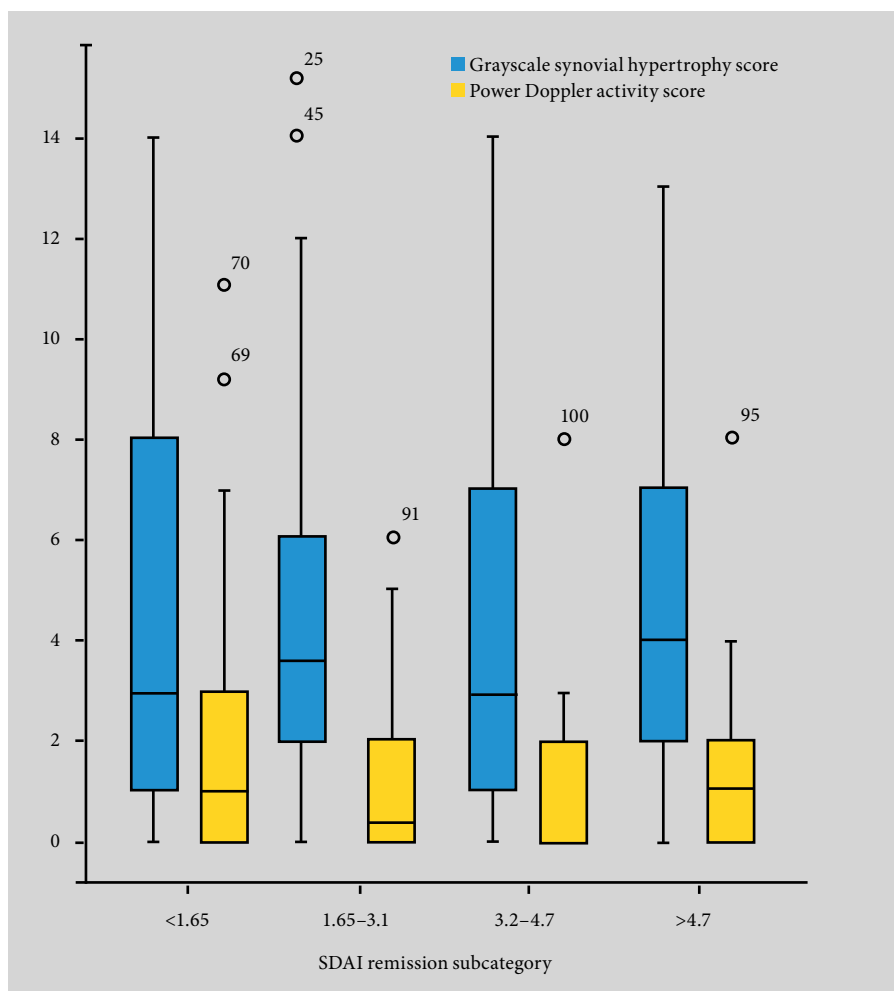


Figure 5.12 The relationship between stringent Simplified Disease Activity Index subcategories of remission and total median power Doppler activity and total median grayscale synovial hypertrophy score per patients as detected by ultrasound. No significant difference was seen between the groups. SDAI, Simplified Disease Activity Index. Reproduced with permission from Saleem et al [28] ©BMJ.

Immunological data in remission		n (%) achieving remission	Exact OR (95% CI)	P-value
Naive (% of CD4 + T cells)	<5.5	2/7 (28.6)	reference	-
	5.5–10.0	3/6 (50.0)	2.32 (0.16–44.95)	0.825
	missing	4/7 (57.1)	3.04 (0.24–55.30)	0.592
	>10.0	7/7 (100.0)	14.29 (1.45–∞)	0.021
IRC (% of CD4 + T cells)	>44	1/8 (12.5)	reference	-
	28–44	6/8 (75.0)	16.20 (1.09–1099)	0.041
	missing	3/3 (100.0)	12.27 (1.02–∞)	0.048
	<28	6/8 (75.0)	16.20 (1.09–1099)	0.041
T _{reg} CD25 ^{high} FOXP3 ⁺ (% of CD4 + T cells)	>2.2	2/10 (20.0)	reference	-
	1.5–2.2	6/9 (66.7)	7.03 (0.73–111.80)	0.110
	missing	1/1 (100.0)	2.67 (0.07–∞)	0.546
	<1.5	7/7 (100.0)	23.26 (2.54–∞)	0.004
CD62L + T _{reg} (% of CD25 ^{high} FOXP3 ⁺ + T _{reg})	<60	1/5 (20.0)	reference	-
	60–70	5/6 (83.3)	13.45 (0.60–1175)	0.134
	missing	6/11 (54.6)	4.36 (0.29–354.80)	0.462
	>70	4/5 (80.0)	10.91 (0.45–979)	0.206

Table 5.7 Univariate analysis of immunological predictors of sustained remission. Exact odds ratio [OR] and confidence interval [CI]. CD4, cluster of differentiation 4; FOXP3, forkhead box P3; IRC, inflammation-related cells; T_{reg}, regulatory T cells. Reproduced with permission from Saleem et al [3] ©BMJ.

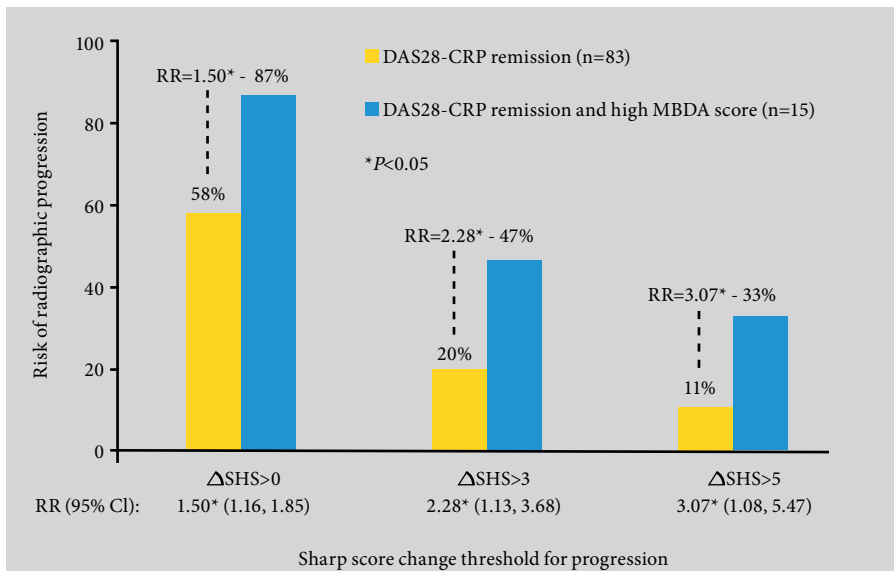


Figure 5.13 A high multi-biomarker disease activity score for subjects in 28-joint disease activity and C-reactive protein score remission indicates increased risk of radiographic progression. CI, confidence interval; DAS28-CRP, 28-joint disease activity and C-reactive protein score; MBDA, multi-biomarker disease activity; RR, response rate; SHS, Sharp/van der Heijde score. Reproduced with permission from van der Helm-van Mil et al [39] ©OUP.

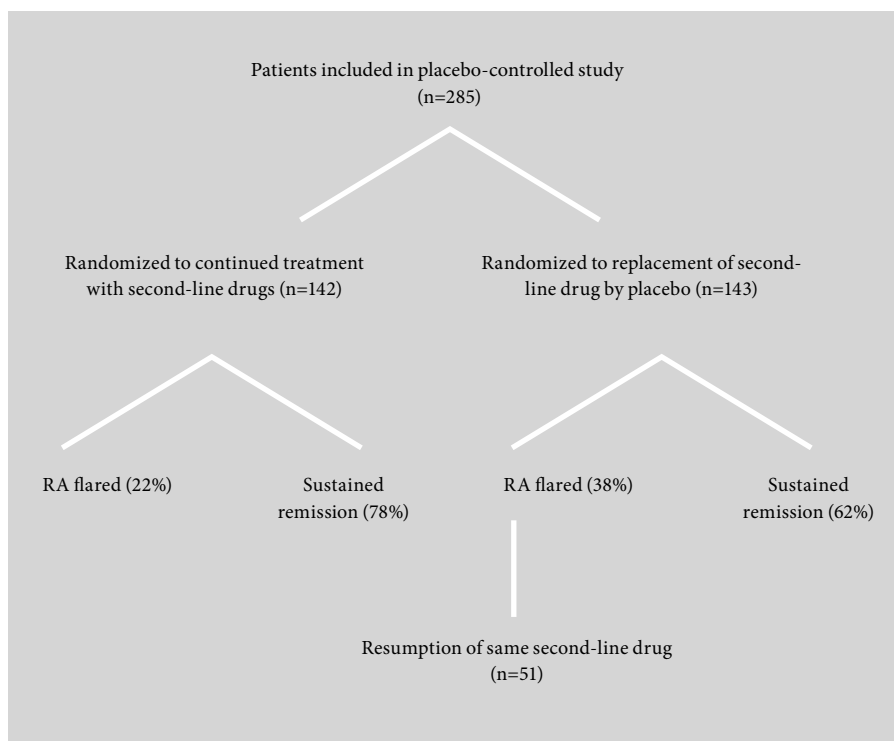


Figure 5.14 Flow diagram illustrating patient numbers and percentages at all stages of the placebo-controlled treatment discontinuation study until the inclusion of 51 patients whose disease flared into the present second-line treatment resumption study. RA, rheumatoid arthritis. Reproduced with permission from ten Wolde et al [45] ©BMJ.

	Sequential monotherapy n=126 (%)	Step-up therapy n=121 (%)	Initial combination with prednisone n=133 (%)	Initial combination with infliximab n=128 (%)
Drug-free indefinitely	31	24	24	36
Still drug-free at 5 years	14 (45)	14 (58)	10 (42)	21 (58)
Restarted DMARD monotherapy	15 (48)	9 (38)	14 (58)	15 (42)
Lost to follow-up	2 (6)	1 (4)	0 (0)	0 (0)

Table 5.8 Overview of the distribution of patients who achieved drug-free remission. DMARD, disease-modifying antirheumatic drug. Data are presented as n (%).

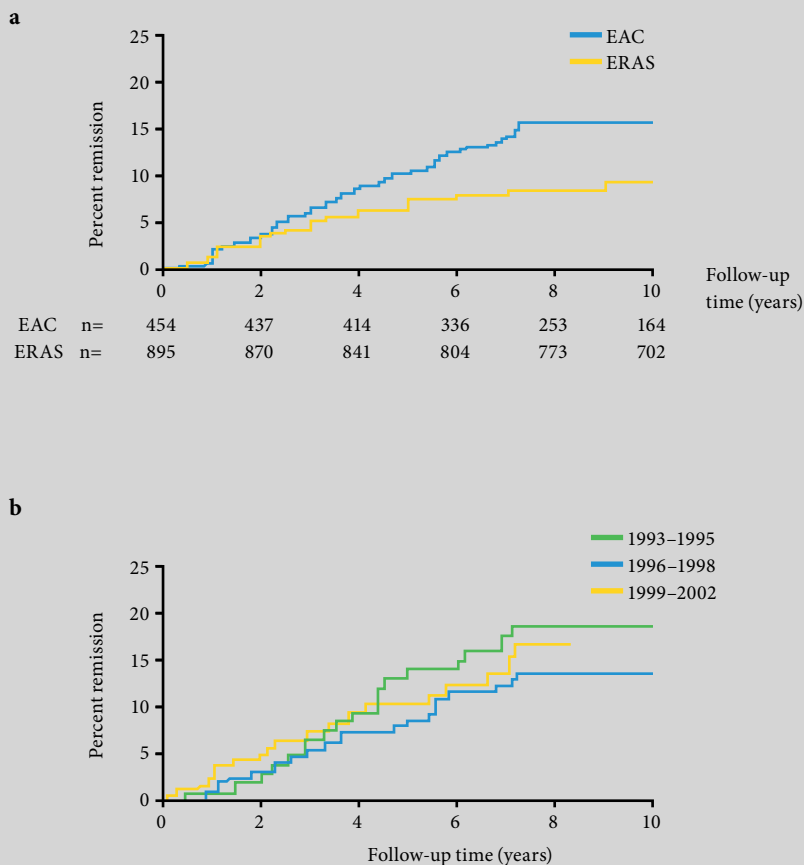


Figure 5.15 Predictors of sustained disease-modifying antirheumatic drug-free remission. (a) Kaplan-Meier curves of the percentage of patients with sustained disease-modifying antirheumatic drug (DMARD)-free remission in the Leiden Early Arthritis Clinic (EAC) cohort compared with the British Early Rheumatoid Arthritis Study (ERAS) cohort. (b) Kaplan-Meier curves of the percentage of patients in the Leiden EAC cohort with sustained DMARD-free remission, stratified by period of inclusion. Differences between the different strata were not significant ($P=0.52$ by log rank test across all strata). The line representing the patients included from 1999 until 2002 terminates at 8 years of follow-up because this was the maximum follow-up for patients in this stratum (data were collected in 2007). Reproduced with permission from van der Woude et al [46] ©Wiley.

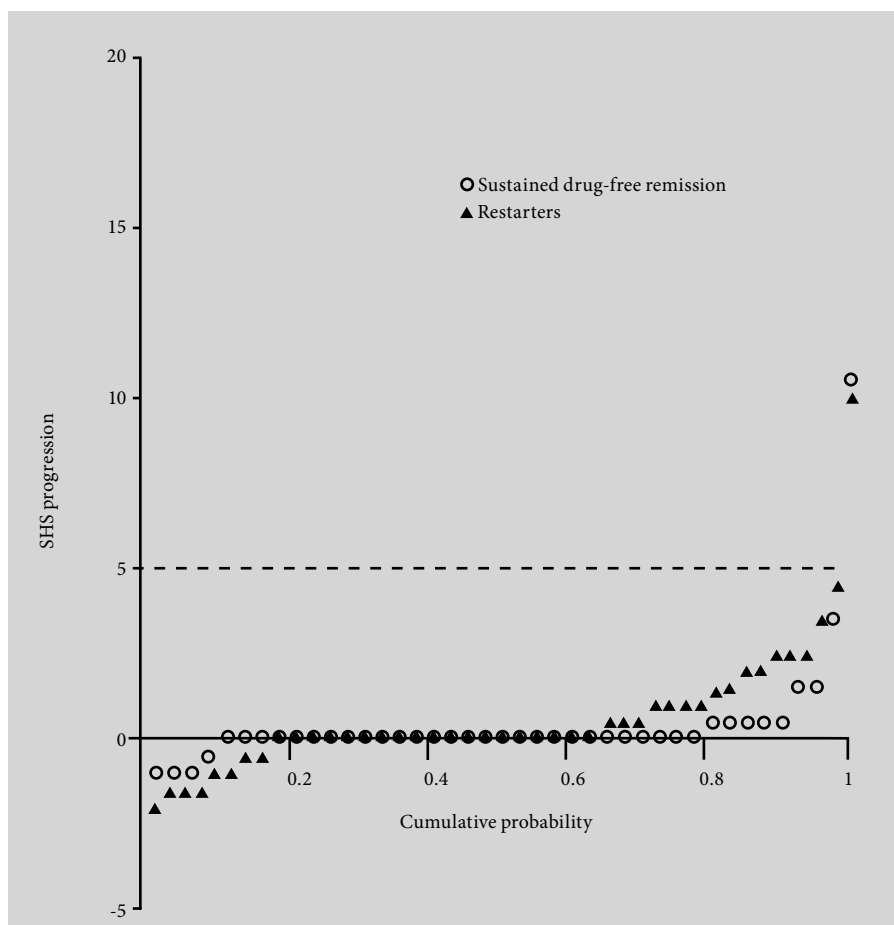


Figure 5.16 Cumulative probability plot showing radiological joint damage progression in the first year after stopping the last disease-modifying antirheumatic drugs. Patients who remained in clinical remission (circles) versus patients who restarted treatment (triangles). The dashed line represents clinically relevant progression. SHS, Sharp-van der Heijde score.

Clinical features	Sustained remission (n=19)	Flare (n=28)	P-value
Disease duration until treatment (months)	18 (15–22)	72 (22–207)	<0.0001
HAQ	0 (0–0)	0.5 (0–1.6)	0.012
RAQoL	0 (0–2)	3 (0–11.5)	0.039

Table 5.9 Clinical characteristics in patients that sustained remission compared to those that flared after stopping tumor necrosis factor-blocker therapy. HAQ, Health Assessment Questionnaire; RAQoL, Rheumatoid Arthritis Quality of Life Questionnaire. Reproduced with permission from Saleem [3] ©BMJ.

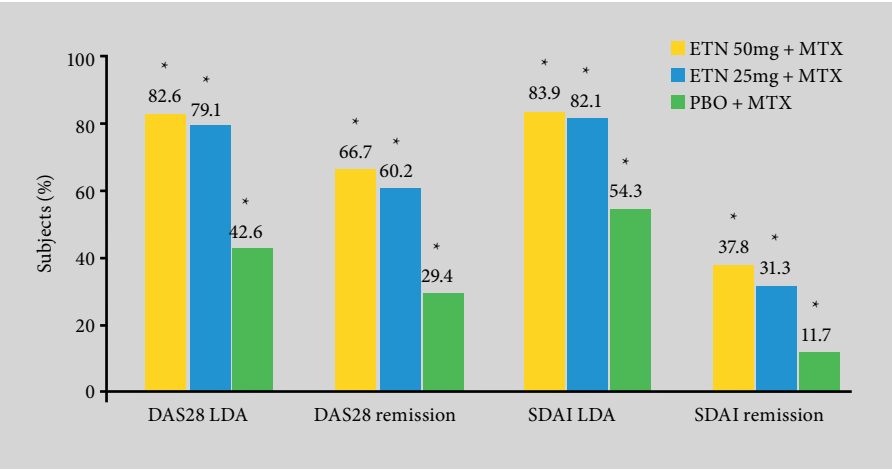


Figure 5.16 The proportion of patients in remission and low disease activity at week 88. DAS28, disease activity in 28 joints; ETN, etanercept; LDA, low disease activity; MTX, methotrexate; PBO, placebo; SDAI, simple disease activity index. Adapted with permission from Smolen et al [49] ©Lancet.

References

1. Aletaha D. Nothing lasts forever – a critical look at sustained remission. *Arthritis Res Ther.* 2012;14:116.
2. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis.* 2011;69:964-975.
3. Saleem B, Keen H, Goeb V, et al. Patients with RA in remission on TNF blockers: when and in whom can TNF blocker therapy be stopped? *Ann Rheum Dis.* 2010;69:1636-1642.
4. Aletaha D, Nell VP, Stamm T, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. *Arthritis Res Ther.* 2005;7:R796-R806.
5. Pinals RS, Masi AT, Larsen RA. Preliminary criteria for clinical remission in rheumatoid arthritis. *Arthritis Rheum.* 1981;24:1308-1315.
6. Sokka T, Makinen H, Hannonen P, Pincus T. Most people over age 50 in the general population do not meet ACR remission criteria or OMERACT minimal disease activity criteria for rheumatoid arthritis. *Rheumatology (Oxford).* 2007; 46:1020-1023.
7. van der Heijde DM, van 't Hof MA, van Riel PL, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann Rheum Dis.* 1990;49:916-920.
8. Ritchie DM, Boyle JA, McInnes JM, et al. Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. *Q J Med.* 1968;37:393-406.
9. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum.* 1995;38:44-48.
10. Smolen JS, Breedveld FC, Schiff MH, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. *Rheumatology (Oxford).* 2003;42:244-257.
11. Smolen JS, Aletaha D. What should be our treatment goal in rheumatoid arthritis today? *Clin Exp Rheumatol.* 2006;24(6 Suppl 43):S7-S13.
12. Felson DT, Smolen JS, Wells G, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann Rheum Dis.* 2011;70:404-413.
13. Lillegraven S, Prince FH, Shadick NA, et al. Remission and radiographic outcome in rheumatoid arthritis: application of the 2011 ACR/EULAR remission criteria in an observational cohort. *Ann Rheum Dis.* 2012;71:681-686.
14. Landewe R, van der Heijde D, van der Linden S, Boers M. Twenty-eight-joint counts invalidate the DAS28 remission definition owing to the omission of the lower extremity joints: a comparison with the original DAS remission. *Ann Rheum Dis.* 2006;65:637-641.
15. Kapral T, Dernoschnig F, Machold KP, et al. Remission by composite scores in rheumatoid arthritis: are ankles and feet important? *Arthritis Res Ther.* 2007;9:R72.
16. Landewe R, van der Heijde D, Klareskog L, van Vollenhoven R, Fatenejad S. Disconnect between inflammation and joint destruction after treatment with etanercept plus methotrexate: results from the trial of etanercept and methotrexate with radiographic and patient outcomes. *Arthritis Rheum.* 2006;5:3119-3125.
17. van der Heijde D, Klareskog L, Boers M, et al. Comparison of different definitions to classify remission and sustained remission: 1 year TEMPO results. *Ann Rheum Dis.* 2005;64:1582-1587.
18. Wechalekar MD, Lester S, Proudman SM, et al. Active foot synovitis in patients with rheumatoid arthritis: applying clinical criteria for disease activity and remission may result in underestimation of foot joint involvement. *Arthritis Rheum.* 2011;64:1316-1322.
19. Koski JM, Saarakkala S, Helle M, Hakulinen U, Heikkinen JO, Hermunen H. Power Doppler ultrasonography and synovitis: correlating ultrasound imaging with histopathological findings and evaluating the performance of ultrasound equipments. *Ann Rheum Dis.* 2006;65:1590-1595. Wakefield RJ, Balint PV, Szkudlarek M, et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol.* 2005;32:2485-2487.

20. Gandjbakhch F, Foltz V, Mallet A, Bourgeois P, Fautrel B. Bone marrow oedema predicts structural progression in a 1-year follow-up of 85 patients with RA in remission or with low disease activity with low-field MRI. *Ann Rheum Dis.* 2011;70:2159-2162.
21. Brown AK, Quinn MA, Karim Z, et al. Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. *Arthritis Rheum.* 2006;54:3761-3773.
22. Wakefield RJ, Freeston JE, Hensor EM, Bryer D, Quinn MA, Emery P. Delay in imaging versus clinical response: a rationale for prolonged treatment with anti-tumor necrosis factor medication in early rheumatoid arthritis. *Arthritis Rheum.* 2007;57:1564-1567.
23. Saleem B, Brown AK, Keen H, et al. Disease remission state in patients treated with the combination of tumor necrosis factor blockade and methotrexate or with disease-modifying antirheumatic drugs: A clinical and imaging comparative study. *Arthritis Rheum.* 2009;60:1915-1922.
24. Balsa A, de Miguel E, Castillo C, Peiteado D, Martin-Mola E. Superiority of SDAI over DAS-28 in assessment of remission in rheumatoid arthritis patients using power Doppler ultrasonography as a gold standard. *Rheumatology (Oxford).* 2010;49:683-690.
25. Scire CA, Montecucco C, Codullo V, Epis O, Todoerti M, Caporali R. Ultrasonographic evaluation of joint involvement in early rheumatoid arthritis in clinical remission: power Doppler signal predicts short-term relapse. *Rheumatology (Oxford).* 2009;48:1092-1097.
26. Peluso G, Michelutti A, Bosello S, Gremese E, Toluoso B, Ferraccioli G. Clinical and ultrasonographic remission determines different chances of relapse in early and long standing rheumatoid arthritis. *Ann Rheum Dis.* 2011;70:172-175.
27. Saleem B, Brown AK, Keen H, et al. Should imaging be a component of rheumatoid arthritis remission criteria? A comparison between traditional and modified composite remission scores and imaging assessments. *Ann Rheum Dis.* 2011;70:792-798.
28. Karim Z, Wakefield RJ, Quinn M, et al. Validation and reproducibility of ultrasonography in the detection of synovitis in the knee: a comparison with arthroscopy and clinical examination. *Arthritis Rheum.* 2004;50:387-394.
29. Mulherin D, Fitzgerald O, Bresnihan B. Clinical improvement and radiological deterioration in rheumatoid arthritis: evidence that the pathogenesis of synovial inflammation and articular erosion may differ. *Br J Rheumatol.* 1996;35:1263-1268.
30. Molenaar ET, Voskuyl AE, Dinant HJ, Bezemer PD, Boers M, Dijkmans BA. Progression of radiologic damage in patients with rheumatoid arthritis in clinical remission. *Arthritis Rheum.* 2004;50:36-42.
31. Kirwan JR. The relationship between synovitis and erosions in rheumatoid arthritis. *Br J Rheumatol.* 1997;36:225-228.
32. Brown AK, Conaghan PG, Karim Z, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. *Arthritis Rheum.* 2008;58:2958-2967.
33. Gandjbakhch F, Conaghan PG, Ejbjerg B, et al. Synovitis and osteitis are very frequent in rheumatoid arthritis clinical remission: results from an MRI study of 294 patients in clinical remission or low disease activity state. *J Rheumatol.* 2011;38:2039-2044.
34. Ostergaard M, Peterfy C, Conaghan P, et al. OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI scoring system. *J Rheumatol.* 2003;30:1385-1386.
35. Hetland ML, Ejbjerg B, Horslev-Petersen K, et al. MRI bone oedema is the strongest predictor of subsequent radiographic progression in early rheumatoid arthritis. Results from a 2-year randomised controlled trial (CIMESTRA). *Ann Rheum Dis.* 2009;68:384-390.
36. Saleem B, Brown AK, Quinn et al. Can flare be predicted in DMARD treated RA patients in remission, and is it important? A cohort study. *Ann Rheum Dis.* 2012;71:1316-1321.
37. Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. New therapies for treatment of rheumatoid arthritis. *Lancet.* 2007;370:1861-1874.

38. van der Helm-van Mil AH, Knevel R, Cavet G, Huizinga TW, Haney DJ. An evaluation of molecular and clinical remission in rheumatoid arthritis by assessing radiographic progression. *Rheumatology (Oxford)*. 2013;52:839-846.
39. Cade R, Stein G, Pickering M, Schlein E, Spooner G. Low dose, long-term treatment of rheumatoid arthritis with azathioprine. *South Med J*. 1976;69:388-392.
40. Cats A. A multicentre controlled trial of the effects of different dosage of gold therapy, followed by a maintenance dosage. *Agents Actions*. 1976;6:355-363.
41. De Silva M, Hazleman BL. Long-term azathioprine in rheumatoid arthritis: a double-blind study. *Ann Rheum Dis*. 1981;40:560-563.
42. Ahern MJ, Hall ND, Case K, Maddison PJ. D-penicillamine withdrawal in rheumatoid arthritis. *Ann Rheum Dis*. 1984;43:213-217.
43. ten Wolde S, Breedveld FC, Hermans J, et al. Randomised placebo-controlled study of stopping second-line drugs in rheumatoid arthritis. *Lancet*. 1996;347:347-352.
44. ten Wolde S, Hermans J, Breedveld FC, Dijkmans BA. Effect of resumption of second line drugs in patients with rheumatoid arthritis that flared up after treatment discontinuation. *Ann Rheum Dis*. 1997;56:235-239.
45. van der Woude D, Young A, Jayakumar K, et al. Prevalence of and predictive factors for sustained disease-modifying antirheumatic drug-free remission in rheumatoid arthritis: results from two large early arthritis cohorts. *Arthritis Rheum*. 2009;60:2262-2271.
46. van der Bijl AE, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. Infliximab and methotrexate as induction therapy in patients with early rheumatoid arthritis. *Arthritis Rheum*. 2007;56:2129-2134.
47. Klarenbeek NB, van der Kooij SM, Guler-Yuksel M, et al. Discontinuing treatment in patients with rheumatoid arthritis in sustained clinical remission: exploratory analyses from the BeSt study. *Ann Rheum Dis*. 2011;70:315-319.
48. Smolen JS, Nash P, Durez P, et al. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. *Lancet*. 2013;381:918-929.

PART TWO

Imaging of rheumatoid arthritis

6 Magnetic resonance imaging in rheumatoid arthritis

Mikkel Østergaard, Mette Bjørndal Axelsen, Mikael Boesen

Introduction

Magnetic resonance imaging (MRI) provides multiplanar tomographical imaging with high soft tissue contrast without the use of ionizing radiation and allows assessment of all structures involved in rheumatoid arthritis (RA). MRI is more sensitive than clinical examination and conventional radiography (X-ray) for detecting inflammation and joint damage. Compared to ultrasonography (US), MRI provides better storage and documentation of findings, allowing centralized reading and post-acquisition review by experts, better follow-up for tracking progressive bone damage, and is the only modality to visualize osteitis (bone marrow edema) [1]. Disadvantages of MRI include higher costs and lower availability than radiography, longer examination times, and restriction to a limited anatomical area per session. It should be remembered, however, that costs of MRI are only a small fraction of the cost of biological treatment or the indirect costs of sick leave and early retirement.

Technical aspects

MRI involves no ionizing radiation or increased risk of malignancies and adverse effects of the contrast agents are very rare [1]. However, contrast agent use in case of severely impaired renal function should be avoided due to risk of nephrogenic systemic fibrosis. The generally recommended MRI sequences for use in peripheral RA are:

- T1-weighted (T1w) images in two planes, obtained before and after intravenous gadolinium (Gd)-containing contrast injection (Figures 6.1 and 6.2); and

- a water-sensitive sequence: T2-weighted (T2w) fat-saturated/fat-suppressed (FS) or short tau inversion recovery (STIR) (Figures 6.3–6.5).

Contrast injection is recommended because it increases sensitivity for synovitis in peripheral joints [2,3].

T1w imaging sequences are favored by relatively short imaging times, good anatomical detail, and the ability to visualize tissues with high perfusion and permeability, including the inflamed synovium, after intravenous Gd injection. Fat- and Gd-enhanced tissues have a high signal intensity on T1w images (Figures 6.1–6.6). T2w images depict both fat and fluid/edematous tissues with a high signal intensity (Figure 6.6), and are particularly useful when FS techniques, in which the signal from fat is suppressed (ie, fat appears black), are applied. This allows detection of edematous tissue and fluid located in areas with fatty tissue (eg, bone marrow edema). FS is also frequently applied on T1w images in order to more clearly visualize inflammation in synovium, tendon sheaths, and bursae (Figures 6.6–6.8). FS techniques require a homogenous field and high magnetic field strength (at least 1.0 T), where the spectral separation between fat and water is sufficiently large. However, the STIR technique (Figure 6.3–6.8), which is based on relaxation time differences and is available on low field units, can provide comparable information [4].

Dedicated extremity MRI units (E-MRI) are smaller MRI units which can be used to examine peripheral joints. Some E-MRI units provide information on synovitis and bone destruction that is not markedly inferior to what is obtained by standard sequences on high-field units [4,5], but the performance of different machines varies. E-MRI increases the potential for widespread use in clinical rheumatology due to markedly lower costs, more comfortable patient positioning, and elimination of claustrophobia.

Recent developments which may improve the evaluation of RA are dynamic contrast-enhanced MRI (Figures 6.9 and 6.10), which may provide a more accurate assessment of inflammation and, thereby, constitute a better disease activity measure [6,7]. Whole-body MRI may allow examination and screening of all peripheral and axial sites in the body in one MRI examination (Figure 6.11) [8].

Visualizing rheumatoid arthritis

MRI allows assessment of all the structures involved in RA, including synovial membrane, intra- and extra-articular fluid collection, cartilage, bone, ligaments, tendons, and tendon

sheaths (Figures 6.1–6.8). MRI and histopathological and miniarthroscopical signs of synovial inflammation are closely correlated [9,10]. MRI bone marrow edema (Figures 6.5 and 6.7) represents inflammatory infiltrates in the bone marrow (ie, osteitis), as demonstrated by comparison with histological samples obtained at surgery in patients with RA [11,12]. Whereas erosions reflect bone damage that has already occurred, bone marrow edema appears to represent the link between joint inflammation and bone destruction. A high level of agreement for detection of bone erosions in wrists and metacarpophalangeal joints affected by RA (concordance at 77–90% of sites) between MRI and CT, using CT as the gold standard reference for detection of bony destruction, documents that MRI erosions represent true bone damage [13,14].

For the cervical spine, the primary imaging modality is CR, but MRI can provide detailed information on bone and soft tissue abnormalities, which can be a valuable supplement to radiographic evaluation (Figures 6.12–6.14) [15]. For example, MRI is able to directly visualize the synovium around the odontoid process (Figures 6.13 and 6.14). Cord compression seen on MRI, mainly due to instability in and around the odontoid process, has proven a better predictor for deterioration than initial clinical and conventional radiographic findings [16].

Diagnosing rheumatoid arthritis

Two large follow-up studies of undifferentiated arthritis have documented an independent predictive value of MRI in the diagnosis of RA [17,18]. Presence of bone edema had a positive predictive value of 86.1% for subsequent development of RA and a prediction model using clinical hand arthritis, morning stiffness, positive rheumatoid factor, and MRI bone edema score in metatarsophalangeal and wrist joints correctly identified the development of RA or non-RA in 82% of patients [17,18].

In the recently revised American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 criteria for RA [19], classification of definite RA is based on the presence of definite clinical synovitis (swelling at clinical examination) in one joint, absence of an alternative diagnosis that better explains the synovitis, and achievement of a total score ≥ 6 (of a possible 10) from the individual scores in four domains. In the joint involvement domain, which can provide up to five of the six points needed for an RA diagnosis, MRI and US synovitis can be used to determine the joint involvement [19–21].

Monitoring disease activity and structural damage

Semiquantitative scoring by the Outcome Measures in Rheumatology (OMERACT) RA MRI scoring system (RAMRIS) of synovitis, bone erosions, and bone edema is the method most often used in observational and randomized clinical trials. It is based on consensus MRI definitions of important joint pathologies and the aforementioned ‘core set’ of basic MRI sequences [3]. A EULAR-OMERACT RA MRI reference image atlas has been developed, providing a easy-to-use tool for standardized RAMRIS scoring [22]. RAMRIS erosion scores are closely correlated with erosion volumes estimated by MRI and CT. The system has good intra- and inter-reader reliability and a high sensitivity to change, demonstrating that the system, after proper training and calibration of readers, is suitable for monitoring joint inflammation and destruction in RA [23]. An MRI joint space narrowing scoring system has also recently been developed [24]. MRI also allows quantitative (eg, volume; or, for synovitis, early contrast enhancement after intravenous contrast injection), as well as qualitative (eg, less detailed: presence/absence) evaluation of synovitis, bone edema, and bone erosions [6,7].

MRI allows for more sensitive monitoring of inflammation (Figures 6.1 and 6.2) and bone erosion than clinical and radiographic assessments [25–28]. A recent study of methotrexate-naïve patients demonstrated that inhibition of erosive progression by biological therapy can be demonstrated by MRI using half as many patients and half of the follow-up time when compared to using radiography [28].

Prognostication

Several studies have demonstrated a predictive value of MRI pathology in wrist and/or MCP joints to radiographic progression. In particular, bone marrow edema is now established as a strong independent predictor of subsequent radiographic progression in early RA [29,30]. Regression analyses in 3-year and 5-year follow-up in the two respective cohorts have documented that MRI bone edema is a predictor of long-term radiographic progression [31,32]. Two small studies have indicated a relationship of baseline MRI findings with long-term functional disability and tendon rupture over a 6-year period [33,34].

MRI synovitis is frequently found in patients in clinical remission (Figure 6.5) and MRI synovitis scores in individual joints are related to progressive radiographic damage at 1-year follow-up [35,36]. This encourages further exploration of using MRI to predict disease course, evaluate disease status, and define imaging remission.

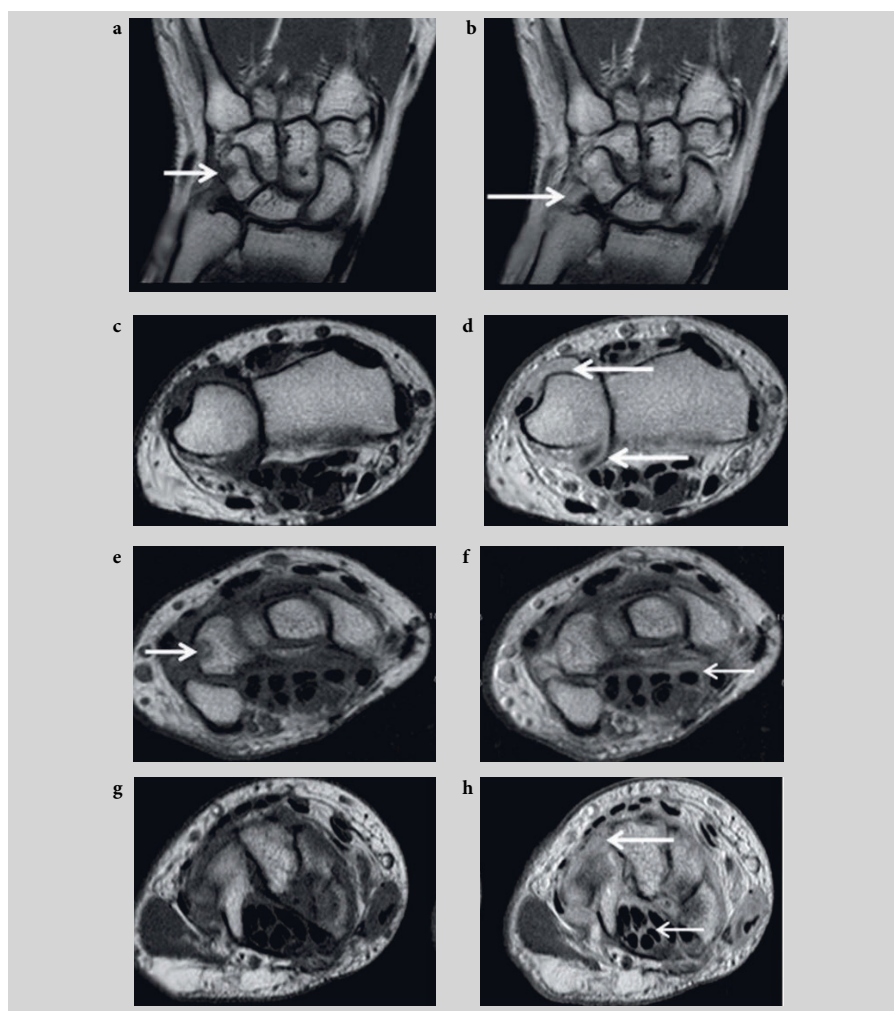


Figure 6.1 Magnetic resonance imaging (MRI) of the wrist of a patient with clinically active early rheumatoid arthritis (<6 months' duration). T1-weighted MRI in the coronal (a, b) and axial planes (c–h), before (left column) and after (right column) intravenous contrast injection. (c, d): Axial section through the distal radius and ulna. (e, f): Section through the proximal row of carpal bones. (g, h): An even more distal section through the hook of the hamate. An erosion is seen in the triquetrum (short thick arrows) in two planes. Marked synovitis is seen both in proximal and distal parts of the wrist joint (long arrows). Furthermore, flexor tenosynovitis is seen (thin short arrows).

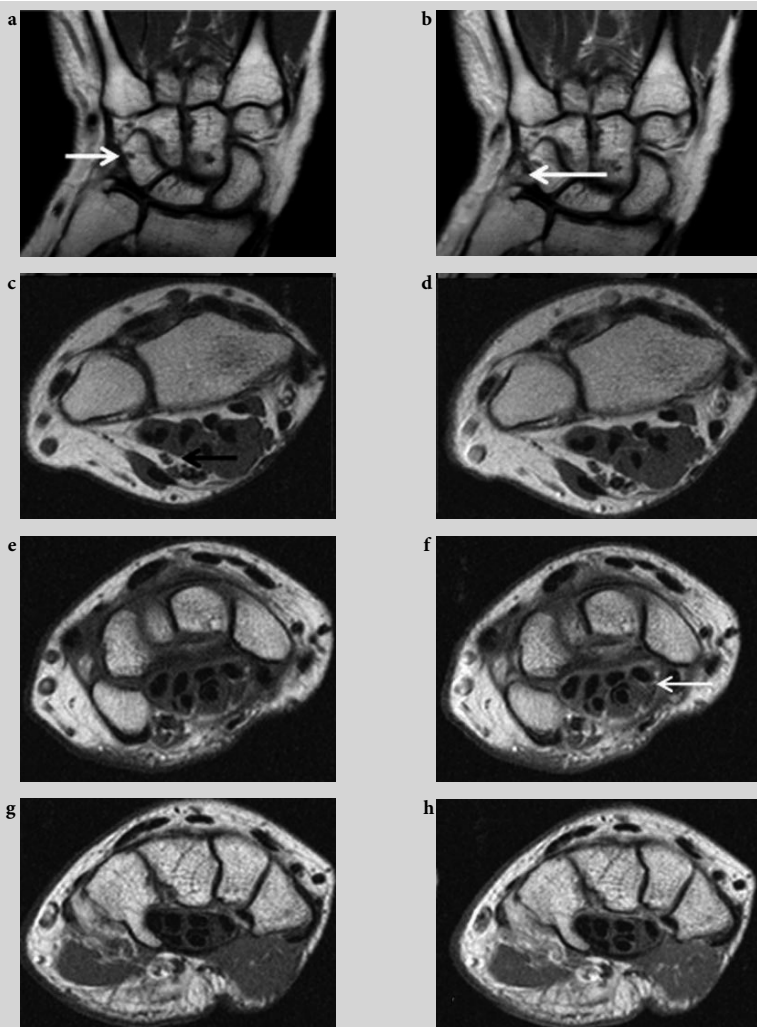


Figure 6.2 Magnetic resonance imaging (MRI) of the wrist of patient with early rheumatoid arthritis after treatment with disease-modifying antirheumatic drug. Same patient as Figure 6.1. T1-weighted MRI in the (a, b) coronal and (c–h) axial planes, before (left column) and after (right column) intravenous contrast injection. (c, d): Axial section through the distal radius and ulna. (e, f): A section through the proximal row of carpal bones. (g, h): A more distal section through the hook of the hamate. The flexor tenosynovitis (thin short arrow) and particularly the synovitis have decreased markedly compared to before treatment (Figure 6.1). The erosion in the triquetrum (short thick arrow) is still seen.

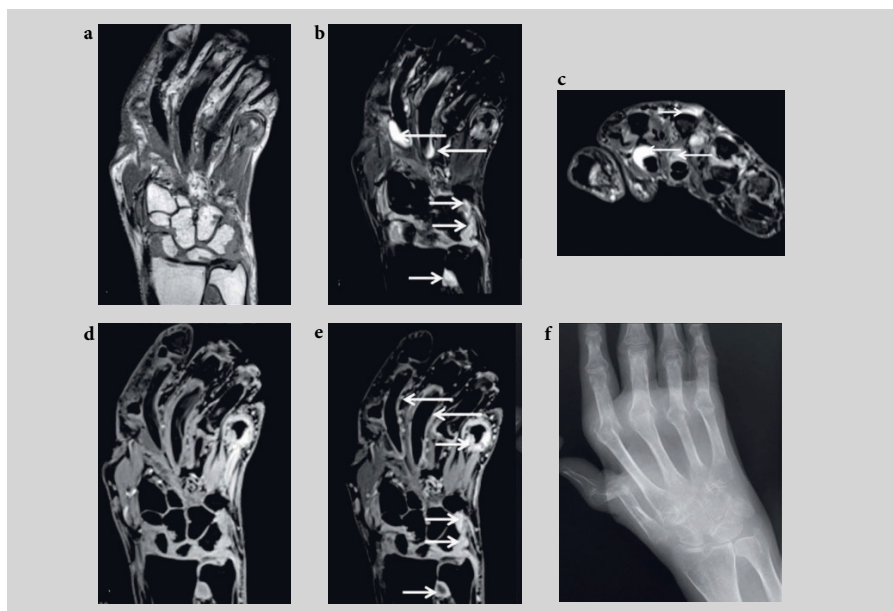


Figure 6.3 Magnetic resonance imaging (MRIs) and X-ray of the hand and wrist of patient with rheumatoid arthritis with ulnar deviation and luxation of the metacarpophalangeal joints due to advanced severe disease. The displayed MRIs are (a) coronal T1-weighted; (b) coronal short tau inversion recovery (STIR) ; (c) axial STIR (through metacarpals); and coronal T1-weighted fat-suppressed before (d) and after (e) intravenous contrast injection. On top of ulnar deviation of the fingers, due to severe damage, MRI reveals marked synovitis in both wrist and metacarpophalangeal (MCP) joints (short arrows), as well as tenosynovitis in the second and third flexor tendons (long arrows). The corresponding hand and wrist X-ray (f) shows severe destruction in the MCP joints.

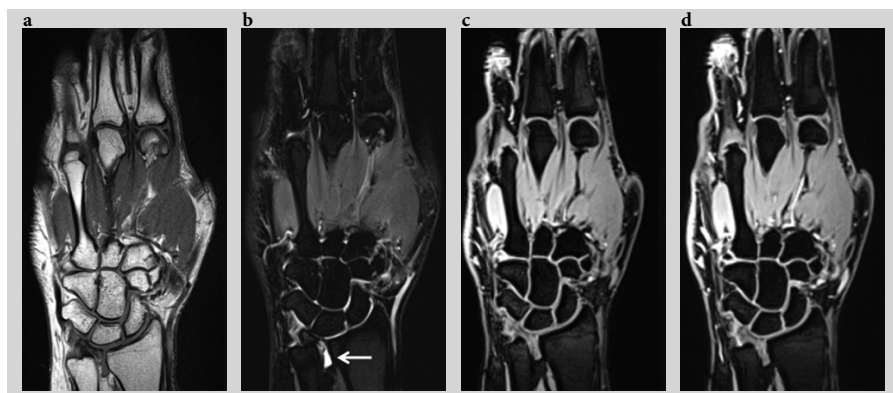


Figure 6.4 Magnetic resonance imaging (MRI) of hand and wrist in a patient with early rheumatoid arthritis in clinical and imaging remission. (a) Coronal T1-weighted; (b) short tau inversion recovery (STIR); and 3D gradient echo T1-weighted images with fat suppression before (c) and after (d) intravenous contrast injection. No synovitis, bone marrow edema, or erosions are seen; only a slight effusion in the radioulnar joint (arrow). Note the homogenous shape and signal from the joint spaces in the visualized wrist and metacarpophalangeal joints, indicating normal cartilage.

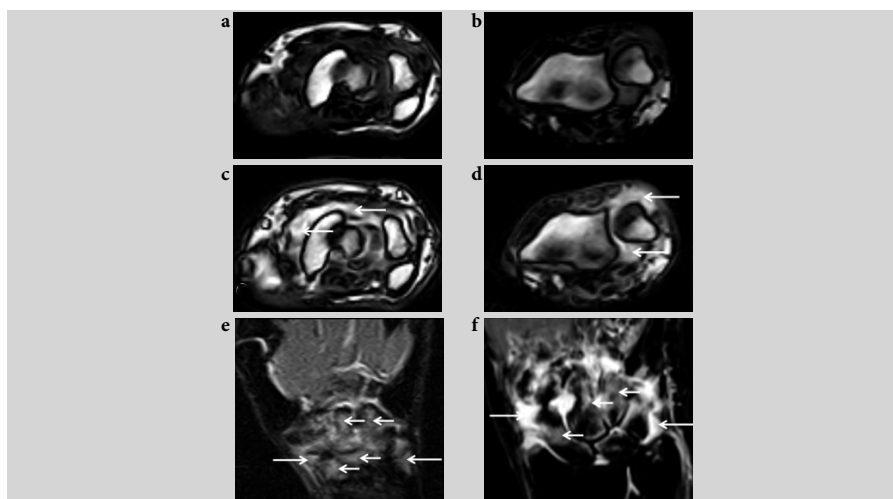


Figure 6.5 Magnetic resonance imaging (MRI) of wrists in patients with clinical remission but not imaging remission. (a–d): Axial T1-weighted MRI before (a–b) and after (c–d) intravenous contrast injection, in sections through the distal radius and ulna (a, c) and through the carpal bones (b, d). The patient is in clinical remission without clinical swelling or tenderness of the joint. Nevertheless, marked synovitis (arrows) is seen; (e) Coronal short tau inversion recovery (STIR) image of another patient in clinical remission, showing synovitis (long arrows) and bone edema (short arrows); (f) Coronal STIR image of another patient with rheumatoid arthritis, showing synovitis (long arrows) and bone edema (short arrows). Images a–e are courtesy of F. Gandjbakhch, Paris, France.

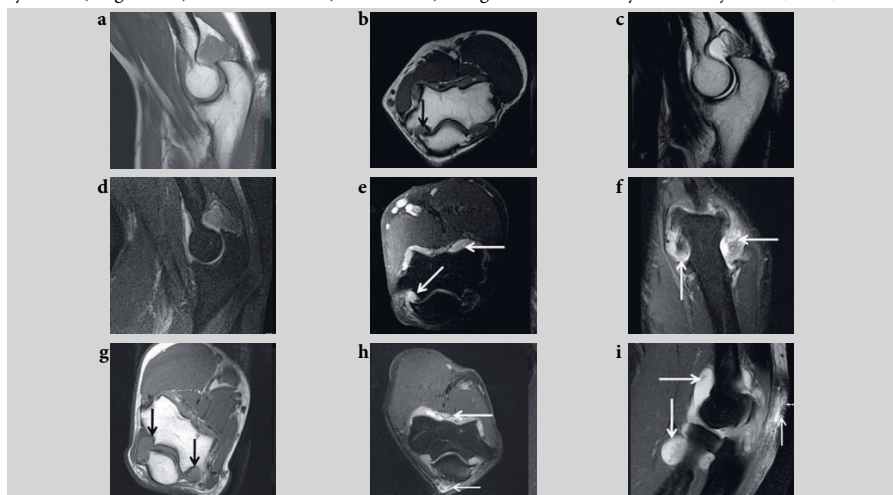


Figure 6.6 Magnetic resonance imaging (MRI) of elbows of a patient with rheumatoid arthritis. (a–f): Left elbow. (a) Sagittal and (b) axial T1-weighted; (c) sagittal T2-weighted; (d) sagittal and (e) axial T1-weighted fat suppressed post-contrast; (f) coronal short tau inversion recovery (STIR) MRI sequences. Images show massive synovitis (thick white arrows) and erosion in the lateral humeral condyle (black arrow). (g–i): Right elbow. (g) Axial T1-weighted; (h) axial STIR; (i) sagittal T1-weighted fat-suppressed image after intravenous contrast injection. Massive synovitis (thick white arrows), erosion in the medial and lateral humeral condyles (g; black arrows), and bursitis olecrani (e, f, h, i; thin white arrows).

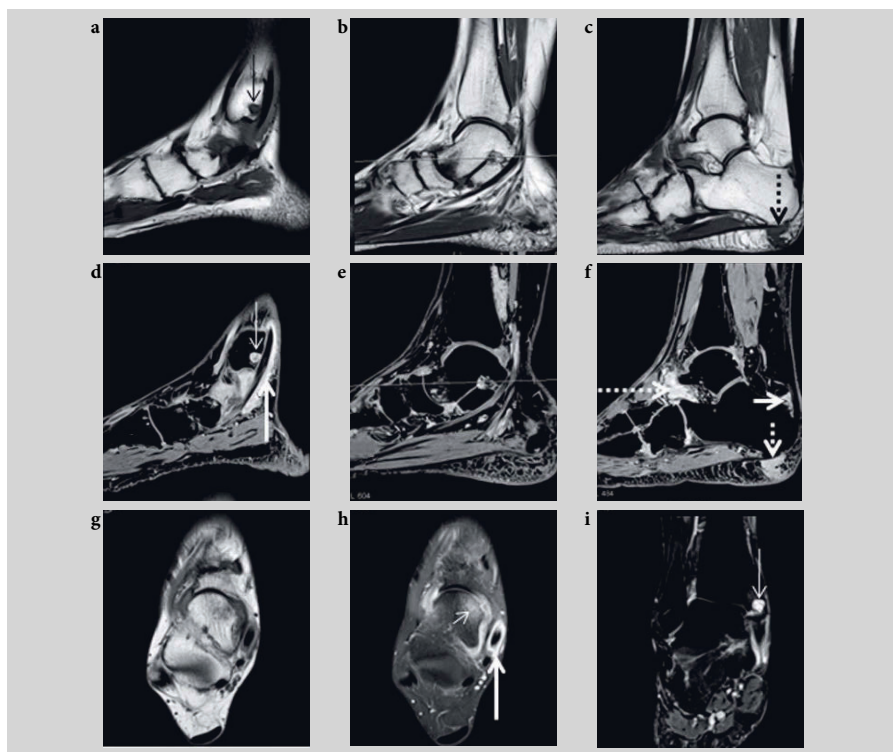


Figure 6.7 Magnetic resonance imaging (MRI) of the ankle and hindfoot of a patient with rheumatoid arthritis. (a–f): Sagittal T1-weighted MRI before (a–c; with fat suppression) and after (d–f; with fat suppression) intravenous contrast injection, through three different sections of the ankle and hindfoot. (g) axial T1-weighted; (h) axial short tau inversion recovery (STIR); (i) coronal STIR MRI. The images show erosion in the medial malleolus (long thin arrow), tenosynovitis at the tibialis posterior tendon (long thick arrows), bursitis in the retrocalcaneal bursa (short thick arrow), synovitis in the ankle joint (long dashed arrow), bone marrow edema in the talus (short thin arrow), and a rheumatoid nodule in the heel fat pad (short dashed arrow).

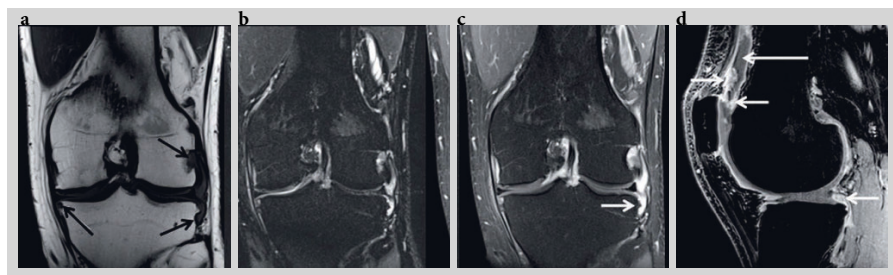


Figure 6.8 Knee of patient with rheumatoid arthritis. (a) Coronal T1-weighted turbo spin echo; (b) short tau inversion recovery (STIR); (c) T1-weighted with fat suppression post-contrast; (d) T1-weighted 3D gradient echo fat suppressed post-contrast sequences, obtained in a 3T MRI unit. Erosion is seen intracapsularly in the 'nude' area at the lateral femoral condyle, as well as at the lateral and medial tibia (black arrows in a). The post-contrast images (c, d) visualize synovitis (short white arrows) and joint effusion (long white arrow).

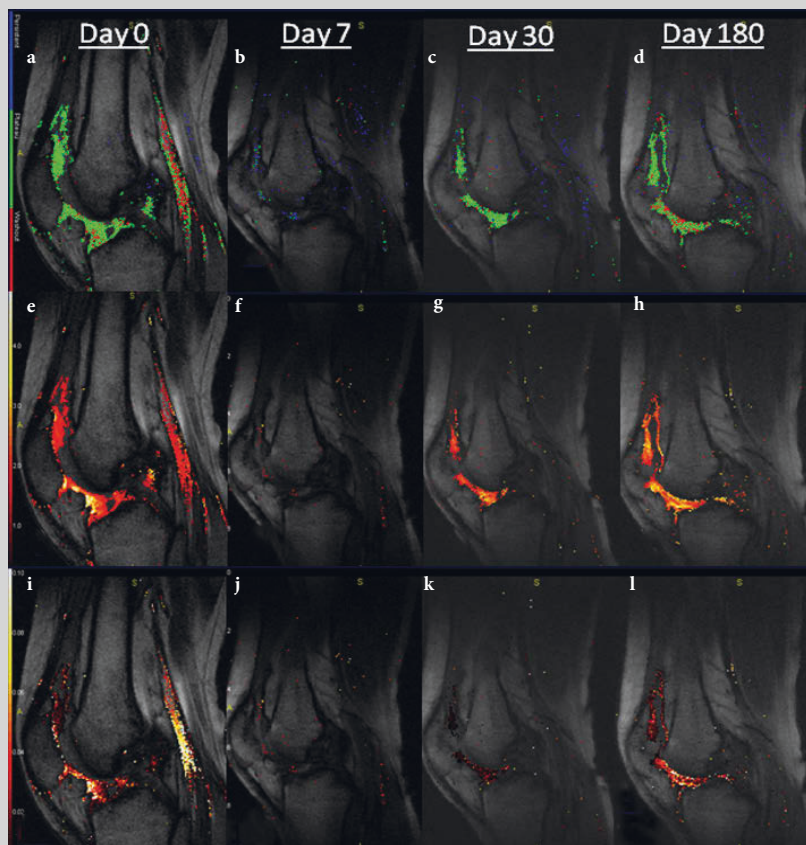


Figure 6.9 Dynamic contrast-enhanced magnetic resonance imaging (MRI) of the knee of a patient with rheumatoid arthritis (RA) before and 7, 30, and 180 days after intra-articular glucocorticoid injection. Using dedicated image processing software (Dynamika, Image Analysis, United Kingdom), color-coded maps of dynamic contrast-enhanced (DCE)-MRI parameters can be super-imposed on the anatomical images. All images are of the knee joint from the same patient with RA, obtained before (a, e, i); at 7 days (b, f, j); at 30 days (c, g, k); and at 180 days (d, h, l) after treatment. In the first row (a–d), all enhancing voxels are color-coded according to their enhancement patterns (persistent [blue], plateau [green], or washout [red]). In the second row (e–h), voxels are color-coded for maximum enhancement (ME; ie, maximum increase in signal intensity [SI] divided by baseline SI). In the third row (i–l), voxels are color-coded for the initial rate of enhancement (percentage increase in SI per second from time of onset of enhancement until ME was reached). Color-codes for each parameter are specified in the vertical bars in the first column. It is noted that the enhancement decreases markedly from baseline (knee clinically swollen) to Day 7 after glucocorticoid injection (knee clinically without signs of inflammation), where after the enhancement parameters gradually increased towards Day 30 (where the knee was still without clinical signs of inflammation) and particularly Day 180 (where the knee had clinically flared).

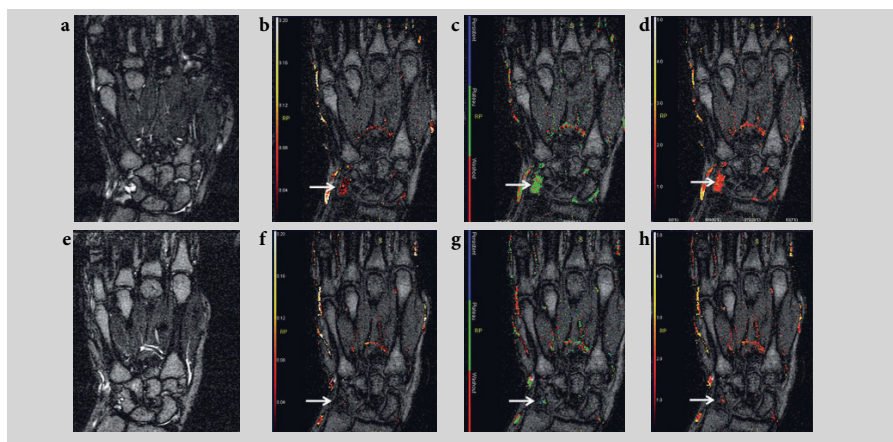


Figure 6.10 Dynamic contrast-enhanced magnetic resonance imaging (MRI) of wrist and 2nd–5th metacarpophalangeal joints of a patient with early rheumatoid arthritis, before and after disease modifying antirheumatic drug therapy. (a,e): Coronal short tau inversion recovery (STIR)-sequence. (b–d; f–h): Dynamic contrast-enhanced MRI obtained before (a–d) and after (e–h) treatment with conventional disease modifying antirheumatic drug therapy (DMARDs). (b, f) Voxels are color-coded according to enhancement pattern: persistent (blue), plateau (green), or washout (red). (c, g) Maximum enhancement (ME; maximum increase in signal intensity [SI] divided by baseline SI); (d, h) initial rate of enhancement (percentage increase in SI per second from time of onset of enhancement ME was reached). It is noted that the enhancement in certain areas of the wrist (radioulnar joint, arrows) decreases markedly during therapy, whereas the enhancement is minimal at both time points in the metacarpophalangeal joints. (Same patient as seen in Figures 6.1 and 6.2).

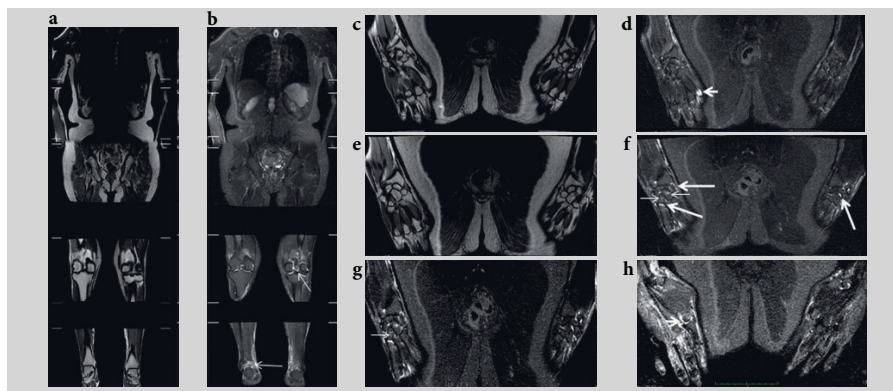


Figure 6.11 Whole-body magnetic resonance imaging (MRI) of a patient with rheumatoid arthritis. Recent MRI hardware and software allow obtaining images of the entire body head-to-toe during one scan session: whole-body MRI (WBMRI). Here, 3T WBMRI are shown. Coronal T1-weighted images without fat suppression before (a) and after (b) with fat suppression after contrast injection are shown (neck and feet are not shown). Synovitis is seen in knee and ankle joints (thin long arrows). (c–f): enlargements of coronal T1-weighted WBMRIs of the hands before (c, e) and after (d, f, with fat suppression) a contrast injection. (g, h): Coronal short tau inversion recovery (STIR) images. Synovitis is seen in both wrists (long thick arrows) and in the right second metacarpophalangeal joint (short thick arrows). Bone marrow edema (d; thin short arrows) is seen in several wrist bones.

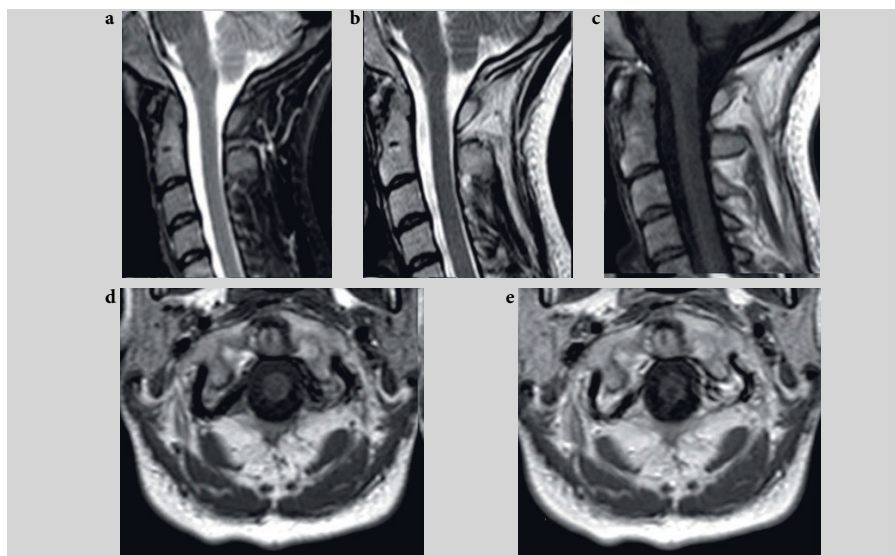


Figure 6.12 Magnetic resonance imaging (MRI) of the normal cervical spine of a patient with early rheumatoid arthritis. Sagittal short tau inversion recovery (STIR) (a); T2-weighted (b); and T1-weighted MRI (c) obtained before Gadolinium contrast injection; axial T1-weighted pre-contrast (d) and post-contrast (e) images. Images show a normal cervical spine. No signs of enhancing pannus or erosions in the C1/C2 junction are seen. Conventional radiographs were normal (not shown).

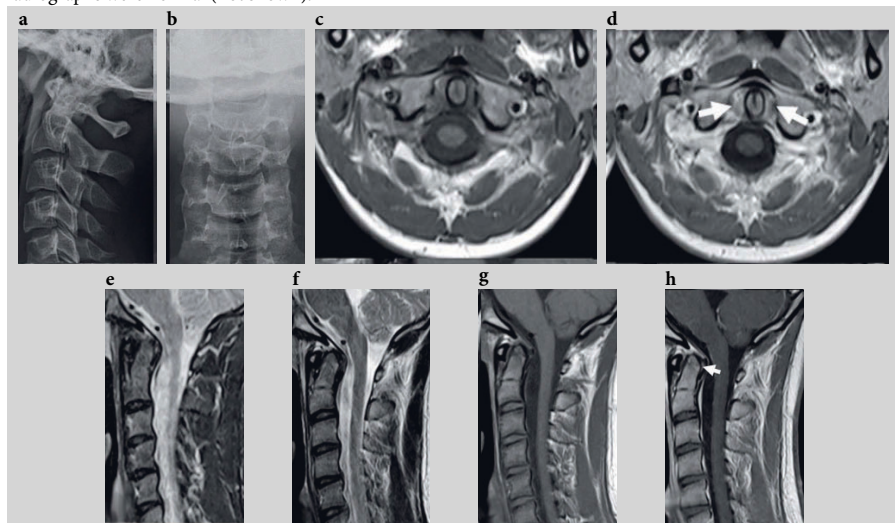


Figure 6.13 Conventional radiograph (X-ray) and magnetic resonance imaging (MRI) of the cervical spine of a patient with rheumatoid arthritis and neck pain. (a, b): Normal X-ray, without signs of C1/C2 luxation and without erosion at dens axis. (c-h): Axial T1-weighted pre-contrast (c) and post-contrast (d) MRI are displayed in the upper row. The lower row displays (e) sagittal T2-weighted; (f) short tau inversion recovery (STIR); (g) pre-contrast T1-weighted; and (h) post-contrast T1-weighted MRI. Enhancing synovitis is seen around the dens axis (arrows). No erosions are seen.

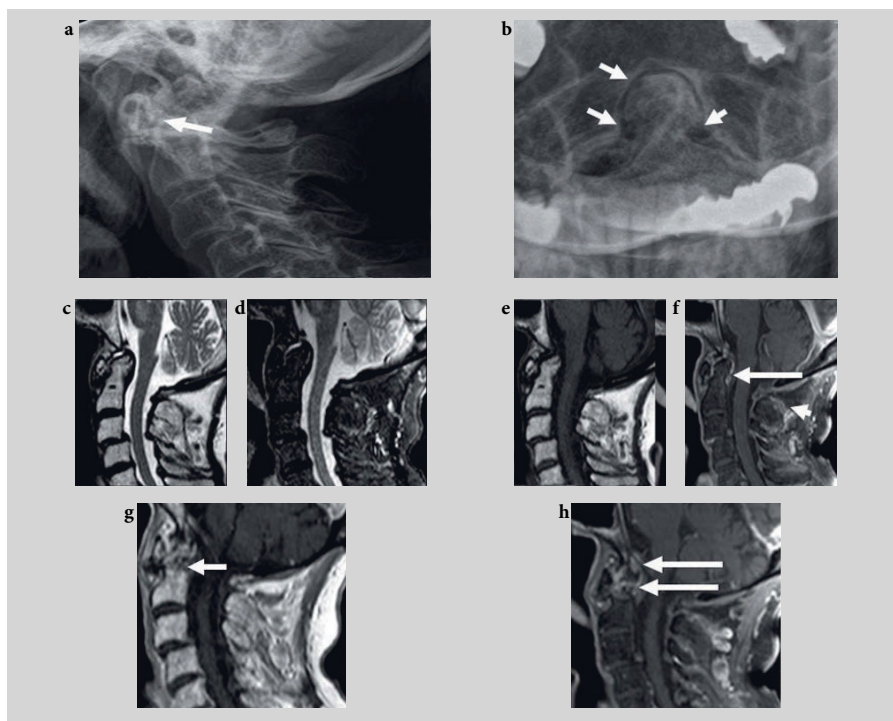


Figure 6.14 Conventional X-ray and magnetic resonance imaging (MRI) of the cervical spine of a patient with rheumatoid arthritis. Upper row: (a) X-ray of the cervical spine in lateral projection shows signs of subluxation (arrow) of the C1/C2 junction; (b) open mouth X-ray of the dens axis shows several erosions (arrows). Middle row: (c) sagittal short tau inversion recovery (STIR); (d) T2-weighted; (e) T1-weighted pre-contrast; (f) T1-weighted post-contrast 1.5T MRI of the upper cervical spine. Lower row: (g) T1-weighted pre-contrast; (h) T1-weighted post-contrast MRI of a neighboring section of the same patient (arrows in the post-contrast T1w images) and marginal erosions of the dens axis (open arrows). Post-contrast images show enhancing synovitis around the dens axis (long arrows). Furthermore, erosions are seen in the dens axis (short arrows).

References

1. Østergaard M, Pedersen SJ, Döhn UM. Imaging in rheumatoid arthritis-status and recent advances for magnetic resonance imaging, ultrasonography, computed tomography and conventional radiography. *Best Pract Res Clin Rheumatol*. 2008; 22:1019-1044.
2. Østergaard M, Peterfy C, Conaghan P, et al. OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI scoring system. *J Rheumatol*. 2003;30:1385-1386.
3. Østergaard M, Conaghan PG, O'Connor P, et al. Reducing invasiveness, duration, and cost of magnetic resonance imaging in rheumatoid arthritis by omitting intravenous contrast injection – Does it change the assessment of inflammatory and destructive joint changes by the OMERACT RAMRIS? *J Rheumatol*. 2009;36:1806-1810.
4. Ejbjerg BJ, Nørvestad E, Jacobsen S, Thomsen HS, Østergaard M. Optimised, low cost, low field dedicated extremity MRI is highly specific and sensitive for synovitis and bone erosions in rheumatoid arthritis wrist and finger joints: comparison with conventional high field MRI and radiography *Ann Rheum Dis*. 2005;64:1280-1287.
5. Taouli B, Zaim S, Peterfy CG, et al. Rheumatoid arthritis of the hand and wrist: comparison of three imaging techniques. *AJR Am J Roentgenol*. 2004;182:937-943.
6. Boesen M, Østergaard M, Cimmino MA, Kubassova O, Jensen KE, Bliddal H. MRI quantification of rheumatoid arthritis: current knowledge and future perspectives. *Eur J Radiol*. 2009;71:189-196.
7. Axelsen MB, Stoltenberg M, Poggenborg RP, et al. Dynamic gadolinium-enhanced magnetic resonance imaging allows accurate assessment of the synovial inflammatory activity in rheumatoid arthritis knee joints: a comparison with synovial histology. *Scand J Rheumatol*. 2012;41:89-94.
8. Kamishima T, Fujieda Y, Atsumi T, et al. Contrast-enhanced whole-body joint MRI in patients with unclassified arthritis who develop early rheumatoid arthritis within 2 years: feasibility study and correlation with MRI findings of the hands. *AJR Am J Roentgenol*. 2010;195:W287-W292.
9. Østergaard M. Magnetic resonance imaging in rheumatoid arthritis. Quantitative methods for assessment of the inflammatory process in peripheral joints. *Dan Med Bull*. 1999;46:313-344.
10. Ostendorf B, Peters R, Dann P, et al. Magnetic resonance imaging and miniarthroscopy of metacarpophalangeal joints: sensitive detection of morphologic changes in rheumatoid arthritis. *Arthritis Rheum*. 2001;44:2492-2502.
11. McQueen FM, Gao A, Østergaard M, et al. High-grade MRI bone oedema is common within the surgical field in rheumatoid arthritis patients undergoing joint replacement and is associated with osteitis in subchondral bone. *Ann Rheum Dis*. 2007;66:1581-1587.
12. Jimenez-Boj E, Nobauer-Huhmann I, Hanslik-Schnabel B, F et al. Bone erosions and bone marrow edema as defined by magnetic resonance imaging reflect true bone marrow inflammation in rheumatoid arthritis. *Arthritis Rheum*. 2007;56:1118-1124.
13. Döhn UM, Ejbjerg BJ, Court-Payen, et al. Are bone erosions detected by magnetic resonance imaging and ultrasonography true erosions? A comparison with computed tomography in rheumatoid arthritis metacarpophalangeal joints. *Arthritis Res Ther*. 2006;8:R110.
14. Döhn UM, Ejbjerg BJ, Hasselquist M, et al. Detection of bone erosions in rheumatoid arthritis wrist joints with magnetic resonance imaging, computed tomography and radiography. *Arthritis Res Ther*. 2008;10:R25.
15. Stiskal MA, Neuhold A, Szolar DH, et al. Rheumatoid arthritis of the craniocervical region by MR imaging: Detection and characterization. *Am J Roentgenol*. 1995;165:585-592.
16. Hamilton JD, Johnston RA, Madhok R, Capell HA. Factors predictive of subsequent deterioration in rheumatoid cervical myelopathy. *Rheumatology (Oxford)*. 2001;40:811-815.
17. Tamai M, Kawakami A, Uetani M, et al. A prediction rule for disease outcome in patients with undifferentiated arthritis using magnetic resonance imaging of the wrists and finger joints and serologic autoantibodies. *Arthritis Rheum*. 2009;61:772-778.
18. Duer-Jensen A, Horslev-Petersen K, Hetland ML, et al. Bone edema on magnetic resonance imaging is an independent predictor of rheumatoid arthritis development in patients with early undifferentiated arthritis. *Arthritis Rheum*. 2011;63:2192-2202.

19. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis.* 2010;69:1580-1588.
20. Østergaard M. Clarification of the role of ultrasonography, magnetic resonance imaging and conventional radiography in the ACR/EULAR 2010 rheumatoid arthritis classification criteria – comment to the article by Aletaha et al. *Ann Rheum Dis.* 2010. BMJ Website. ard.bmj.com/content/69/9/1580.short/reply. Accessed March 6, 2015.
21. Aletaha D, Hawker G, Neogi T, Silman A. Re: Clarification of the role of ultrasonography, magnetic resonance imaging and conventional radiography in the ACR/EULAR 2010 rheumatoid arthritis classification criteria – comment to the article by Aletaha et al. *Ann Rheum Dis.* 2011. E-letter. www.ard.bmj.com/letters?first-index=41&hits=10#content-block. Accessed March 6, 2015.
22. Østergaard M, Edmonds J, McQueen F, et al. The EULAR-OMERACT rheumatoid arthritis MRI reference image atlas. *Ann Rheum Dis.* 2005;64(suppl 1):i2-i55.
23. Haavardsholm EA, Østergaard M, Ejbjerg BJ, et al. Reliability and sensitivity to change of the OMERACT rheumatoid arthritis magnetic resonance imaging score in a multireader, longitudinal setting. *Arthritis Rheum.* 2005;52:3860-3867.
24. Østergaard M, Bøyesen P, Eshed I, et al. Development and preliminary validation of a magnetic resonance imaging joint space narrowing score for use in rheumatoid arthritis: potential adjunct to the OMERACT RA MRI scoring system. *J Rheumatol.* 2011;38:2045-2050.
25. Haavardsholm EA, Østergaard M, Hammer HB, et al. Monitoring anti-TNFalpha treatment in rheumatoid arthritis: responsiveness of magnetic resonance imaging and ultrasonography of the dominant wrist joint compared with conventional measures of disease activity and structural damage. *Ann Rheum Dis.* 2009;68:1572-1579.
26. Ejbjerg BJ, Vestergaard A, Jacobsen S, Thomsen HS, Østergaard M. The smallest detectable difference and sensitivity to change of magnetic resonance imaging and radiographic scoring of structural joint damage in rheumatoid arthritis finger, wrist, and toe joints: a comparison of the OMERACT rheumatoid arthritis magnetic resonance imaging score applied to different joint combinations and the Sharp/van der Heijde radiographic score. *Arthritis Rheum.* 2005;52:2300-2306.
27. Quinn MA, Conaghan PG, O'Connor PJ, et al. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2005;52:27-35.
28. Østergaard M, Emery P, Conaghan PG, et al. Significant improvement in synovitis, osteitis, and bone erosion following golimumab and methotrexate combination therapy as compared with methotrexate alone: A magnetic resonance imaging study of 318 methotrexate-naïve rheumatoid arthritis patients. *Arthritis Rheum.* 2011;63:3712-3722.
29. Haavardsholm EA, Bøyesen P, Østergaard M, Schildvold A, Kvien TK. Magnetic resonance imaging findings in 84 patients with early rheumatoid arthritis: bone marrow oedema predicts erosive progression. *Ann Rheum Dis.* 2008;67:794-800.
30. Hetland ML, Ejbjerg B, Horslev-Petersen K, et al. MRI bone oedema is the strongest predictor of subsequent radiographic progression in early rheumatoid arthritis. Results from a 2-year randomised controlled trial (CIMESTRA). *Ann Rheum Dis.* 2009;68:384-390.
31. Bøyesen P, Haavardsholm EA, Østergaard M, van der Heijde D, Sesseng S, Kvien TK. MRI in early rheumatoid arthritis: synovitis and bone marrow oedema are independent predictors of subsequent radiographic progression. *Ann Rheum Dis.* 2011;70:428-433.
32. Hetland ML, Stengaard-Pedersen K, Junker P, et al. Radiographic progression and remission rates in early rheumatoid arthritis – MRI bone oedema and anti-CCP predicted radiographic progression in the 5-year extension of the double-blind randomised CIMESTRA trial. *Ann Rheum Dis.* 2010;69:1789-1795.
33. Benton N, Stewart N, Crabbe J, Robinson E, Yeoman S, McQueen F. MRI of the wrist in early rheumatoid arthritis can be used to predict functional outcome at 6 years. *Ann Rheum Dis.* 2004;63:555-561.

34. McQueen F, Beckley V, Crabbe J, Robinson E, Yeoman S, Stewart N. Magnetic resonance imaging evidence of tendinopathy in early rheumatoid arthritis predicts tendon rupture at six years. *Arthritis Rheum.* 2005;52:744-751.
35. Brown AK, Conaghan PG, Karim Z, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. *Arthritis Rheum.* 2008;58:2958-2967.
36. Gandjbakhch F, Conaghan PG, Ejbjerg B, et al. Synovitis and osteitis are very frequent in rheumatoid arthritis clinical remission: results from an MRI study of 294 patients in clinical remission or low disease activity state. *J Rheumatol.* 2011;38:2039-2044.

7 Ultrasound imaging in rheumatoid arthritis

Maria Antonietta D'Agostino

Introduction

Detailed physical examination alone can fail to provide a correct diagnosis in patients with painful articular or abarticular manifestations, particularly in those with recent disease onset. In these cases, rheumatologists may need further support to look for joint or tendon involvement and suitably objective imaging technique available in everyday practice that can assist with diagnosing joint involvement has long been awaited. Ultrasound (US) is an easy and accessible imaging technique that can visualize soft tissues and cortical bone defects [1,2]. The main advantages of US are absence of ionizing radiation, economy, and dynamic assessment of joint pathologies. In addition, the rapid improvement in the visualization of superficial structures and of slow flow vessels has permitted a widespread development in rheumatology [3,4]. US plays two major roles in rheumatology:

- an extension of physical examination in everyday clinical practice; and
- an objective reference standard in scientific studies.

When compared to magnetic resonance imaging (MRI), which is considered the gold standard for soft tissue and bone pathologies, US is characterized by several advantages (Table 7.1). The high resolution of the technique permits one to distinguish between degenerative, inflammatory, and destructive changes in intra and extra-articular structures, as well as to guide therapeutic procedures. Additionally, under US guidance, the progression of a needle into the soft tissues towards a selected target area can be carefully controlled. This can lead to improved safety for US-guided injections and

aspirations by avoiding possible damage to peripheral nerves, blood vessels, tendons, and cartilage by the needle tip [5,6].

However, despite these several advantages, the widespread use of US in daily practice and as an outcome measure in clinical and therapeutic trials has been hampered by the perception that it is an unreliable, observer-dependent technique. This is primarily due to the technical and physical characteristics of US and the lengthy formal training that is required.

In order to improve validity and promote greater US use in the rheumatology setting, methodological work on standardization has been done by the Outcome Measures in Rheumatology (OMERACT) US Task Force [7]. Due to this international effort, in recent years, US has shown great utility in the management of rheumatic diseases, especially rheumatoid arthritis (RA) [8,9]. This ongoing work has also permitted the development of standardized consensus definitions for the most common inflammatory pathologies and has demonstrated the high level of reliability of the technique through several inter-observer studies [10–18]. Furthermore, international scientific societies such as European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) now provide standardized training to rheumatologists interested in the clinical use of US [19].

Ultrasound and rheumatoid arthritis

Ultrasound-detected synovitis

One of the most common applications of US in RA is the evaluation of joint involvement both for diagnosis and follow-up after therapeutic procedures. The inflammatory process can involve all synovial tissues (ie, diarthrodial joints, synovial tendon sheaths, and synovial bursae), which can be easily visualized using US. Several studies have demonstrated that US is more sensitive than clinical examination for detecting synovitis, with a comparable sensitivity when MRI is considered as a reference [16–18, 20–25]. Overall, the main advantage of US is the capability to assess all aspects of the synovial inflammation due to the ability to evaluate the morphology and quantity of synovitis by using grayscale and its vascularity by using color or power Doppler (PD).

In grayscale, US-detected synovitis is characterized by the swelling of synovial lining (eg, hypoechoic synovial hypertrophy), which can be associated with an increase of synovial fluid (eg, anechoic area) especially in large joints, and an increased perfusion of the lining (eg, hyperemia, shown by PD). The appearance of synovitis in grayscale can vary according

to the duration and activity of the inflammatory process (from anechoic-hypoechoic when inflammation is very active to isohyperechoic when the fibrous tissue become prevalent). US is therefore able to distinguish between active and inactive (eg, fibrous) synovial hypertrophy. The concomitant use of PD technique permits to easily visualize vascularity. The color information given by the Doppler technique is superimposed on the grayscale image in a real-time evaluation of all parameters.

The level of grayscale synovitis correlates well with the disease duration, probably reflecting the level of previous inflammation and subsequent fibrotic change. By contrast, the presence of PD seems independent of disease duration and therefore appears to be a better marker of inflammation at any given time point. This has attracted particular attention because of the possibility of predicting response to treatment, subsequent structural damage, and flare [26]. In addition, a minimal amount of synovial hypertrophy in grayscale can be seen also in normal joints not affected by RA, whilst PD is a rare finding in normal joints. Quantification of US-detected synovitis at joint level can be performed in several ways: Figure 7.1 describes the most common scoring systems for grading synovitis; Figure 7.2 shows the position of the probe and of the hand for the evaluation of small joints synovitis and cartilage involvement; and Figures 7.3–7.6 show examples of US-detected synovitis in small joints. The main consequence of a chronic synovitis is structural damage at cartilage, bony cortex (ie, erosions), and tendon level. The involvement of these structures is accurately visualized by US.

Ultrasound-detected erosions

US erosion can be defined as a discontinuity of the cortical surface. To avoid artifacts, the cortical defect should be seen in at least two perpendicular planes (Figure 7.7). The accuracy of US for detecting erosions has been compared to X-ray, MRI, and computed tomography (CT) scans [27–30]. All of these studies have demonstrated a comparable sensitivity and specificity when MRI or CT (even micro-CT) are used as comparators [30]. The lack of a complete agreement is mostly due to the inaccessibility of the entire bone surface to the US beams (ie, lack of acoustic window such as on the medial and lateral facets of the third and fourth metacarpal heads).

US resolution quality is very high and it is usually possible to see very small erosions (≥ 1 mm). However, specificity as an early marker of structural damage has not yet been definitively demonstrated. In addition, a standardized scoring system for erosions has not yet been developed. At the moment, the position of the erosions, their size, and the concomitant

presence of an active synovitis (Figure 7.8) are used to determine whether they are related to the RA process.

Ultrasound-detected tenosynovitis

In addition to intra-articular synovitis, tenosynovitis is a common pathologic feature in RA [1]. The proliferation of the tenosynovium can produce tendon adhesion and rupture with consequent severe joint function impairment [31]. US-detected tenosynovitis is defined by the presence of abnormal hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath, which is seen in two perpendicular planes and which may exhibit Doppler signal. Normal tendons with synovial sheath can show a minimal, well defined, and homogeneous peritendinous halo which corresponds to normal synovial sheath. The presence of peritendinous PD signal within the synovial sheath should be confirmed in two perpendicular planes, exclude normal feeding vessels (ie, PD signal displayed by vessels at the mesotenon or vinculae), and be present only if the tendon shows peritendinous synovial sheath widening on grayscale. Long-standing tenosynovitis can be characterized by concomitant lesions in the body of a tendon. Figures 7.9–7.11 are examples of US scans showing tenosynovitis.

Cartilage damage

A wide range of joint cartilage lesions can be detected by US. Normal hyaline cartilage appears as a homogeneously anechoic band delimited by two well-defined, sharp, hyperechoic margins [32]. These features are basically the same at different anatomic sites. Echotexture inhomogeneity due to patchy increment of echogenicity can be regarded as an early sign of a cartilage lesion, while the loss of sharpness associated with decrease of the normal thickness can be seen as advanced sign of involvement. Diffuse narrowing or complete disappearance are advanced signs of disease (Figure 7.12).

Management of rheumatoid arthritis with ultrasound: diagnosis, therapeutic follow-up, remission, and flare

US has demonstrated the ability to accurately detect synovitis even in an early stage of disease when most of the inflammatory joint involvement is subclinical [33,34]. In particular, the detection of PD signal seems important for predicting RA [35]. In daily practice, US is a useful tool for following up with patients undergoing treatment for RA. Several studies

have demonstrated that US is a sensitive tool for following patients under treatment; Table 7.2 shows recently published studies demonstrating high sensitivity to change (both grayscale and PD) independently of the scoring system used at joint level or the number of joints examined [25,36–41].

Persistent inflammation in RA is known to lead to cartilage and bone destruction, and grayscale and PD synovitis are a reflection of inflammation. US has been shown to be an important tool for evaluating if patients are genuinely in remission or in a low-activity disease state [42]. Several studies have shown that the presence of subclinical US synovitis (mostly PD, but also grayscale synovitis) is a predictive factor for a disease flare and radiographic structural progression in patients with RA in clinical remission.

Conclusion

As previously discussed, there is evidence to support the routine use of US in the management of RA and wider implementation may have major implications for the diagnosis and treatment of RA. However, some questions still need to be clarified and require further research, including the specific importance of grayscale and Doppler components, the scoring of US synovitis at joint and patient level (ie, scoring systems and minimal joint count), and the minimal threshold of synovitis in RA remission.

Ultrasound		MRI	
Strengths	Weaknesses	Strengths	Weaknesses
Real-time and dynamic imaging	Unable to image within bone	Ability to image bone	Limited to one body region
Immediately accessible; complements the physical examination	Specialist training not always available	More complete assessment of whole joint (all articular surfaces)	Potential for motion artifact and contraindications (eg, pacemaker)
Relatively easy to examine multiple body regions	Limited accessibility of some fractures (acoustic window)	Quantitative measurement of synovium	Time and patient tolerance

Table 7.1 Comparative assessment of the advantages and limitations of ultrasound and magnetic resonance imaging (MRI) for the management of rheumatic diseases. In patients with rheumatoid arthritis, the ability to evaluate several joints by ultrasound and detect the presence of active synovial disease or minimal structural damage (ie, detecting small erosions) is a major advantage, as it may reduce the time between disease investigation and treatment initiation. In cases where ultrasound does not detect erosive disease, a complementary MRI is suitable.

Grading of synovitis	
Grayscale • Present/absent • Semi-quantitative (0–3) • Quantitative (0–3) - volume/depth of tissue	Doppler • Semi-quantitative (0–3) • Number of colour pixels in a region of interest (ROI) • Resistance indices (RI) • Time intensity curves (bubble contrast) - measure maximum rate of enhancement - lacks feasibility for multiple joints

Figure 7.1 Most commonly used ultrasound scoring systems at joint level.



Figure 7.2 The position of the hand of an ultrasound probe for examining and evaluating synovitis in small joints. Neutral position of a finger in a (a) longitudinal and (b) transverse scan. (c) Hand is semi-flexed for evaluating cartilage involvement.

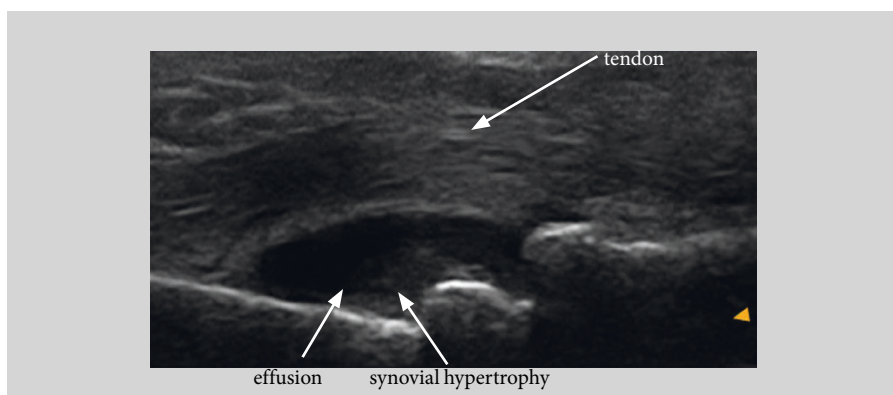


Figure 7.3 Longitudinal palmar scan of metacarpophalangeal joint: grayscale ultrasound. Presence of effusion (anechoic) and hypoechoic synovial hypertrophy compatible with exudative synovitis.

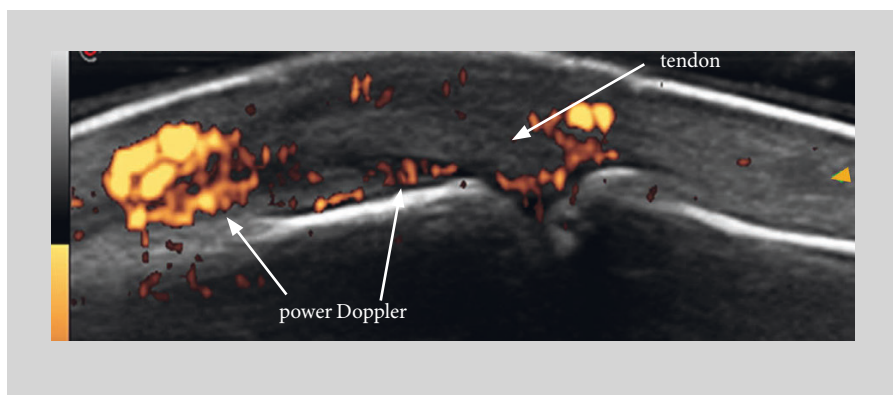


Figure 7.4 Longitudinal dorsal scan of metacarpophalangeal joint: grayscale and power Doppler ultrasound. Presence of hypoechoic synovial hypertrophy that exhibits power Doppler signal. This aspect is typical of severe synovitis.

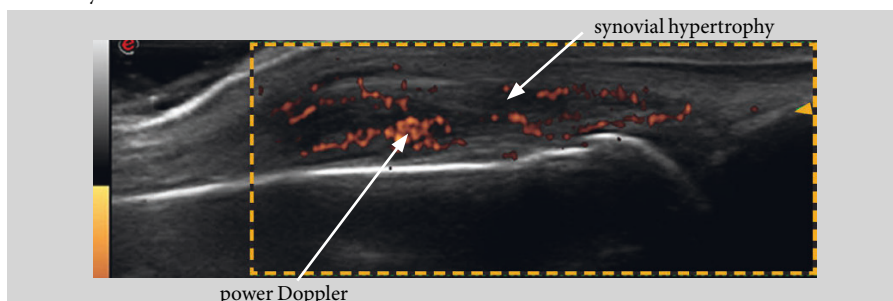


Figure 7.5 Longitudinal dorsal scan of metacarpophalangeal joint: grayscale and power Doppler ultrasound. Presence of hypoechoic synovial hypertrophy which exhibits power Doppler signal. This aspect is typical of a moderate synovitis.

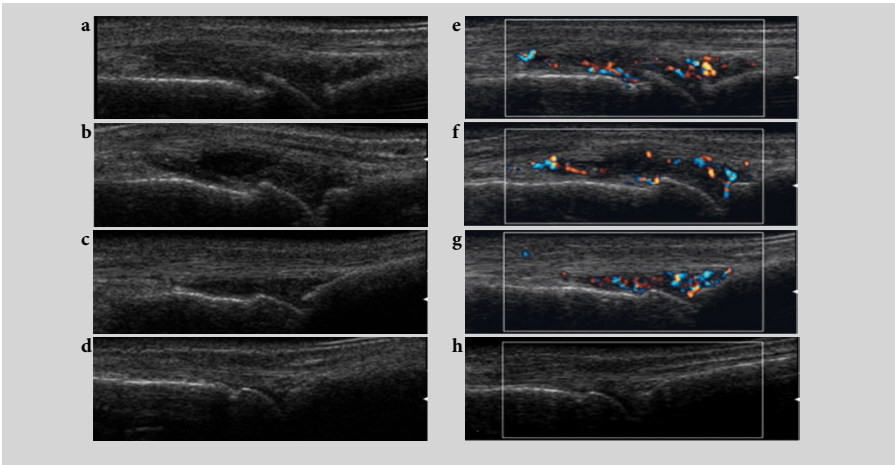


Figure 7.6 This ultrasound picture shows a longitudinal dorsal scan of four metacarpophalangeal joints with different grade of synovitis. Panels a–d show the grayscale appearance, whereas panels e–h show the same joints when power Doppler is applied.

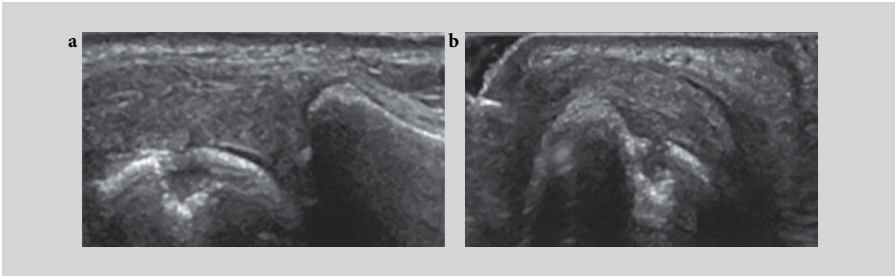


Figure 7.7 Ultrasound detected erosion of a metacarpal head in a dorsal (a) longitudinal and (b) transverse scan.

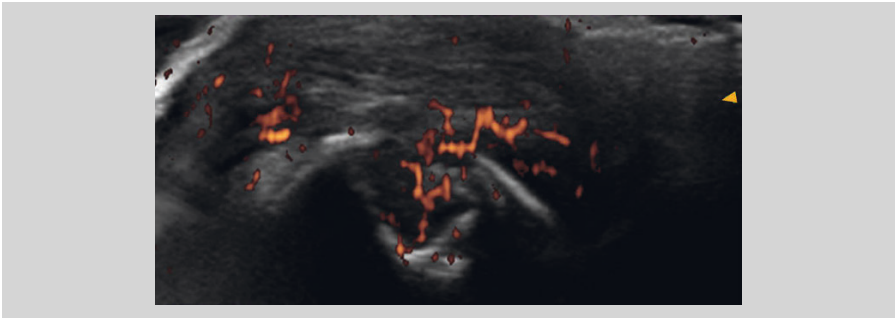


Figure 7.8 Ultrasound-detected erosion of a metacarpal head in a dorsal longitudinal with associated inflammatory synovitis (both grayscale and power Doppler).

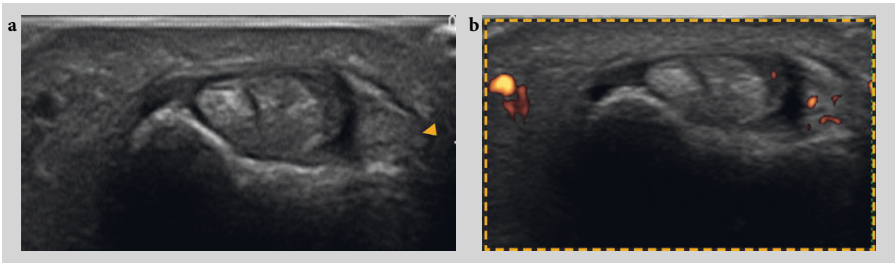


Figure 7.9 An ultrasound normal aspect of extensor ulnaris carpi in a transverse scan. (a) Grayscale alone. (b) Normal power Doppler signal due to normal feeding vessels within tendon sheet.

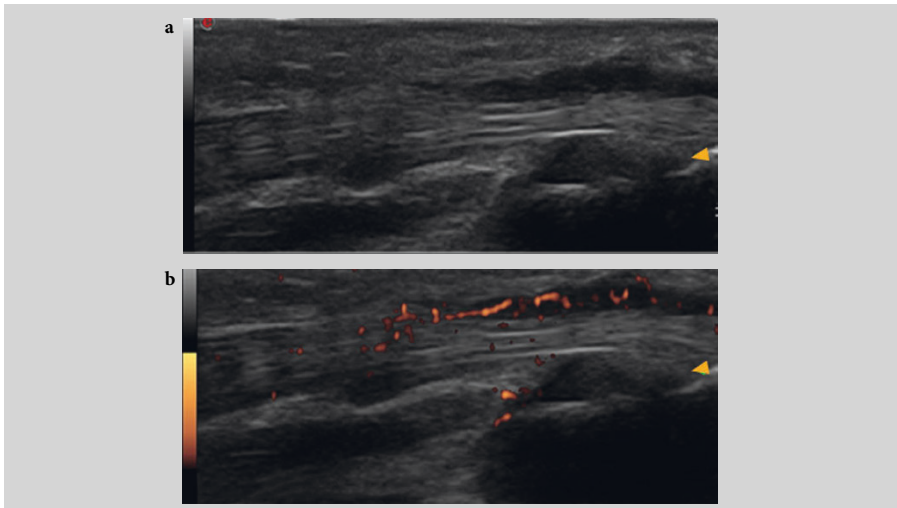


Figure 7.10 Ultrasound longitudinal scan of extensor ulnaris carpi. (a) Minimal tenosynovitis in grayscale. (b) Minimal tenosynovitis with power Doppler signal within tendon sheet.

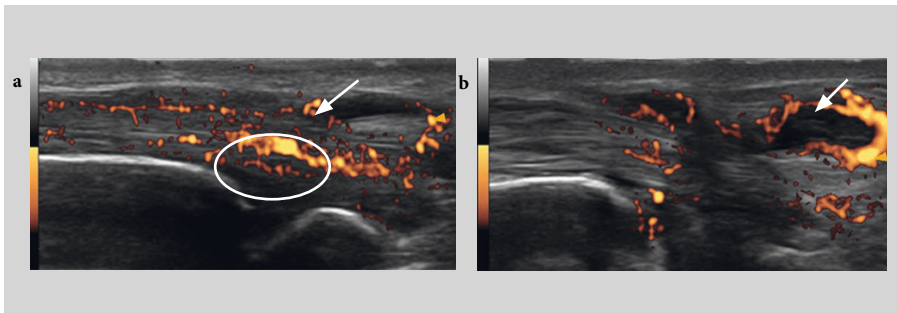


Figure 7.11 Examples of ultrasound longitudinal scan of extensor ulnaris carpi. Severe tenosynovitis in both grayscale and power Doppler signal within the tendon sheet (arrows) and inside the tendon (circled).

Grayscale synovitis (SH, SE, both)						
Author, reference	n	Treatment	Follow-up (months)	No. of joints	Score at baseline: mean $\pm$ SD	Score at the end of the study: mean $\pm$ SD (% decrease)
Taylor et al [36]	24	MTX + TNF inhibitor MTX + placebo	3.5	10	14.4 $\pm$ 5.2 14.1 $\pm$ 5.5	6.8 $\pm$ 4.7 (–54.5%) 11.8 $\pm$ 6.8 (–13.7%)
Naredo et al [37]	160	TNF-inhibitor or anakinra	6	44 12	- -	- -
Naredo et al [38]	167	TNF-inhibitor	12	28	16.4 $\pm$ 10.5 15.6 $\pm$ 9.9	8.5 $\pm$ 8.6 8 $\pm$ 8
Iagnocco et al [39]	25	adalimumab	24	10	-	-
Backhaus et al [40]	120	DMARDs or TNF-inhibitor or both	6	7	8.1 $\pm$ 5.8	5.5 $\pm$ 5.5 (–32%)
Dougados et al [41]	76	TNF-inhibitor	4	–28 –20 –38	12.88 $\pm$ 6.20 10.58 $\pm$ 4.02 18.18 $\pm$ 7.07	9.12 $\pm$ 6.19 7.90 $\pm$ 4.35 25 $\pm$ 7.22
Perricone [25]	45	TNF-inhibitor	3	–12 SE –12 SP –6 SE –6 SP	8.71 $\pm$ 6.23 8.27 $\pm$ 6.14 5.71 $\pm$ 3.92 5.80 $\pm$ 4.21	5.84 $\pm$ 4.05 5.47 $\pm$ 4.06 4.00 $\pm$ 2.59 4.07 $\pm$ 2.82

Table 7.2 Published data showing the sensitivity to change of ultrasound independently of the scoring system used and the number of joints examined. Standardized response mean (SRM), the ratio between the mean changes over the standard deviation (SD) of the changes. Usually, a SRM below 0.2 is considered as nul and above 0.6 as relevant. CI, confidence interval; DMARD, disease-modifying antirheumatic drug; IQR, interquartile range; MTX, methotrexate; SE, synovial effusion; SH, synovial hypertrophy; SP, synovial proliferation; TNF, tumor necrosis factor.

		Power Doppler synovitis (Doppler signal)			
Mean decrease (95% CI)	SRM	Score at baseline (mean $\pm$ SD or median IQR)	Score at the end of the study (mean $\pm$ SD or median IQR), (% decrease)	Mean decrease (95% CI)	SRM
-	-	9.072 $\pm$ 6.718	1.228 – 2.421 (–79%)	-	-
-	-	8.212 $\pm$ 6.479	5.130 – 3.865 (–27%)	-	-
-	-	16.4 $\pm$ 10.9	8.8 $\pm$ 7.8	7.4 (6.0–8.9)	-
-	-	-	-	4.9 (4.1–5.7)	-
8 (6.7–9.2) 7 (6.4–8.8)	–0.881	9.0 $\pm$ 7.2	3.8 $\pm$ 5.0	5.1 (4.3–5.9)	–0.717
-	-	11(4–19)	6.1 (1–15)	-	-
-	-	3.3 $\pm$ 4.0	2.0 $\pm$ 3.5 (–39%)	-	-
-	–0.64 $\pm$ 0.13	7.00 $\pm$ 5.39	4.16 $\pm$ 3.93	-	–0.62 $\pm$ 0.13
-	–0.60 $\pm$ 0.12	5.28 $\pm$ 4.13	2.76 $\pm$ 2.76	-	–0.69 $\pm$ 0.16
-	–0.64 $\pm$ 0.14	9.15 $\pm$ 6.30	5.16 $\pm$ 4.55	-	–0.70 $\pm$ 0.15
-	-	4.36 $\pm$ 5.44	2.67 $\pm$ 3.38	-	-
-	-	3.62 $\pm$ 4.35	2.16 $\pm$ 2.69	-	-
-	-				
-	-				

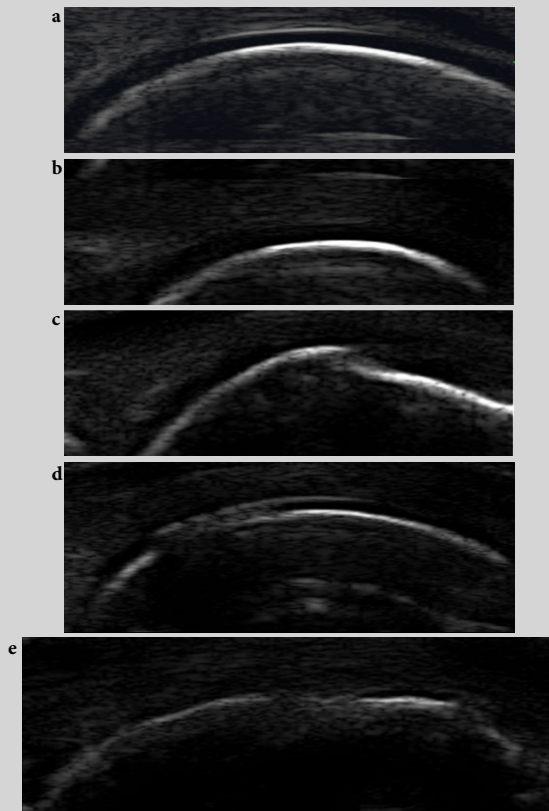


Figure 7.12 Ultrasound findings of cartilage involvement in a longitudinal dorsal scan of metacarpophalangeal joint. (a) Normal aspect; (b) heterogeneous echotexture and/or loss of sharpness; (c) blurring of anterior or posterior interface; (d) asymmetric thinning; (e) complete loss of cartilage.

References

1. Grassi W, Salaffi F, Filippucci E. Ultrasound in rheumatology. *Best Pract Res Clin Rheumatol*. 2005;19:467-485.
2. D'Agostino MA, Breban M. Ultrasonography in inflammatory joint disease: why should rheumatologists pay attention? *Joint Bone Spine*. 2002;69:252-255.
3. Conaghan PG, Ostergaard M, D'Agostino MA, et al. Proceedings from the 5th Annual International Society for Musculoskeletal Imaging in Rheumatology Annual Conference. *Semin Arthritis Rheum*. 2013;42:433-446.
4. Colebatch AN, Edwards CJ, Ostergaard M, et al. EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. *Ann Rheum Dis*. 2013;72:804-814.
5. D'Agostino MA, Ayral X, Baron G, Ravaud P, Breban M, Dougados M. Impact of ultrasound imaging on local corticosteroid injections of symptomatic ankle, hind-, and mid-foot in chronic inflammatory diseases. *Arthritis Rheum*. 2005;53:284-292.
6. D'Agostino MA, Schmidt WA. Ultrasound-guided injections in rheumatology: actual knowledge on efficacy and procedures. *Best Pract Res Clin Rheumatol*. 2013;27:283-294.
7. Wakefield RJ, D'Agostino MA, Iagnocco A, et al. The OMERACT Ultrasound Group: status of current activities and research directions. *J Rheumatol*. 2007;34:848-51.
8. Naredo E, Wakefield RJ, Iagnocco A, et al. The OMERACT ultrasound task force--status and perspectives. *J Rheumatol*. 2011;38:2063-2067.
9. D'Agostino MA, Conaghan PG, Naredo E, et al. The OMERACT ultrasound task force -- advances and priorities. *J Rheumatol*. 2009;36:1829-1832.
10. Wakefield RJ, Balint PV, Szkudlarek M, et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol*. 2005;32:2485-2487.
11. D'Agostino MA, Filippucci E, Backhaus, et al. Intra- and inter-observer reliability of ultrasonography for detecting and scoring synovitis in rheumatoid arthritis: a report of a EULAR ESCISIT Task Force. *Ann Rheum Dis*. 2005;64(suppl III):62.
12. D'Agostino MA, Backhaus M, Balint PV, et al. Combined evaluation of influence of sonographer and machine type on the reliability of power Doppler ultrasonography (PDUS) for detecting, scoring and scanning synovitis in rheumatoid arthritis (RA) patients: results of an intermachine reliability exercise of the EULAR/OMERACT US group. *Ann Rheum Dis*. 2008;67(suppl 2):421.
13. D'Agostino MA, Backhaus M, Balint PV, et al. Evaluation of the intra- and inter-reader reliability of power Doppler ultrasonography (PDUS) for detecting and scoring synovitis of several joints in rheumatoid arthritis (RA) by using a validated scoring system : a report of a the EULAR/OMERACT US group. *Ann Rheum Dis*. 2008;67(suppl 2):422.
14. Naredo E, D'Agostino MA, Wakefield RJ, et al. Reliability of a consensus-based ultrasound score for tenosynovitis in rheumatoid arthritis. *Ann Rheum Dis*. 2013;72:1328-1334.
15. Naredo E, Moller I, Moragues C, et al. Interobserver reliability in musculoskeletal ultrasonography: results from a "Teach the Teachers" rheumatologist course. *Ann Rheum Dis*. 2006;65:14-19.
16. Bruyn GA, Moller I, Garrido J, et al. Reliability testing of tendon disease using two different scanning methods in patients with rheumatoid arthritis. *Rheumatology (Oxford)*. 2012;51:1655-1661.
17. Bruyn GA, Naredo E, Moller I, et al. Reliability of ultrasonography in detecting shoulder disease in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2009;68:357-361.
18. Bruyn GA, Pineda C, Hernandez-Diaz C, et al. Validity of ultrasonography and measures of adult shoulder function and reliability of ultrasonography in detecting shoulder synovitis in patients with rheumatoid arthritis using magnetic resonance imaging as a gold standard. *Arthritis Care Res (Hoboken)*. 2010;62:1079-1086.
19. Naredo E, D'Agostino MA, Conaghan PG, et al. Current state of musculoskeletal ultrasound training and implementation in Europe: results of a survey of experts and scientific societies. *Rheumatology (Oxford)*. 2010;49:2438-2443.

20. Backhaus M, Kamradt T, Sandrock D, et al. Arthritis of the finger joints: a comprehensive approach comparing conventional radiography, scintigraphy, ultrasound, and contrast-enhanced magnetic resonance imaging. *Arthritis Rheum.* 1999;42:1232-1245.
21. Szkudlarek M, Court-Payen M, Strandberg C, Klarlund M, Klausen T, Ostergaard M. Contrast-enhanced power Doppler ultrasonography of the metacarpophalangeal joints in rheumatoid arthritis. *Eur Radiol.* 2003;13:163-168.
22. Szkudlarek M, Court-Payen M, Strandberg C, Klarlund M, Klausen T, Ostergaard M. Power Doppler ultrasonography for assessment of synovitis in the metacarpophalangeal joints of patients with rheumatoid arthritis: a comparison with dynamic magnetic resonance imaging. *Arthritis Rheum.* 2001;44:2018-2023.
23. Wakefield RJ, Freeston JE, O'Connor P, et al. The optimal assessment of the rheumatoid arthritis hindfoot: a comparative study of clinical examination, ultrasound and high field MRI. *Ann Rheum Dis.* 2008;67:1678-1682.
24. Naredo E, Collado P, Cruz A, et al. Longitudinal power Doppler ultrasonographic assessment of joint inflammatory activity in early rheumatoid arthritis: predictive value in disease activity and radiologic progression. *Arthritis Rheum.* 2007;57:116-124.
25. Perricone C, Ceccarelli F, Modesti M, et al. The 6-joint ultrasonographic assessment: a valid, sensitive-to-change and feasible method for evaluating joint inflammation in RA. *Rheumatology (Oxford).* 2013;51:866-873.
26. Brown AK, Conaghan PG, Karim Z, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. *Arthritis Rheum.* 2008;58:2958-2967.
27. Wakefield RJ, Gibbon WW, Conaghan PG, et al. The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography. *Arthritis Rheum.* 2000;43:2762-2770.
28. Szkudlarek M, Klarlund M, Narvestad E, et al. Ultrasonography of the metacarpophalangeal and proximal interphalangeal joints in rheumatoid arthritis: a comparison with magnetic resonance imaging, conventional radiography and clinical examination. *Arthritis Res Ther.* 2006;8:R52.
29. Ostergaard M, Dohn UM, Ejbjerg BJ, McQueen FM. Ultrasonography and magnetic resonance imaging in early rheumatoid arthritis: recent advances. *Curr Rheumatol Rep.* 2006;8:378-385.
30. Dohn UM, Ejbjerg BJ, Court-Payen M, et al. Are bone erosions detected by magnetic resonance imaging and ultrasonography true erosions? A comparison with computed tomography in rheumatoid arthritis metacarpophalangeal joints. *Arthritis Res Ther.* 2006;8:R110.
31. Lillegren S, Boyesen P, Hammer HB, et al. Tenosynovitis of the extensor carpi ulnaris tendon predicts erosive progression in early rheumatoid arthritis. *Ann Rheum Dis.* 2011;70:2049-2050.
32. Filippucci E, da Luz KR, Di Geso L, et al. Interobserver reliability of ultrasonography in the assessment of cartilage damage in rheumatoid arthritis. *Ann Rheum Dis.* 2010;69:1845-1848.
33. Filer A, de Pablo P, Allen G, et al. Utility of ultrasound joint counts in the prediction of rheumatoid arthritis in patients with very early synovitis. *Ann Rheum Dis.* 2011;70:500-507.
34. Funck-Brentano T, Gandjbakhch F, Etchepare F, et al. Prediction of radiographic damage in early arthritis by sonographic erosions and power Doppler signal: a longitudinal observational study. *Arthritis Care Res (Hoboken).* 2013;65:896-902.
35. Salaffi F, Ciapetti A, Gasparini S, et al. Comparison of the Recent-Onset Arthritis Disability questionnaire with the Health Assessment Questionnaire disability index in patients with rheumatoid arthritis. *Clin Exp Rheumatol.* 2010;28:855-865.
36. Taylor PC, Steuer A, Gruber J, et al. Comparison of ultrasonographic assessment of synovitis and joint vascularity with radiographic evaluation in a randomized, placebo-controlled study of infliximab therapy in early rheumatoid arthritis. *Arthritis Rheum.* 2004;50:1107-1116.
37. Naredo E, Rodriguez M, Campos C, et al. Validity, reproducibility, and responsiveness of a twelve-joint simplified power doppler ultrasonographic assessment of joint inflammation in rheumatoid arthritis. *Arthritis Rheum.* 2008;59:515-522.

38. Naredo E, Möller I, Cruz A, Carmona L, Garrido J. Power Doppler ultrasonographic monitoring of response to anti-tumor necrosis factor therapy in patients with rheumatoid arthritis. *Arthritis Rheum.* 2008;58:2248-2256.
39. Iagnocco A, Filippucci E, Perella C, et al. Clinical and ultrasonographic monitoring of response to adalimumab treatment in rheumatoid arthritis. *J Rheumatol.* 2008;35:35-40.
40. Backhaus M, Ohrndorf S, Kellner H, et al. Evaluation of a novel 7-joint ultrasound score in daily rheumatologic practice: a pilot project. *Arthritis Rheum.* 2009;61:1194-1201.
41. Dougados M, Jousse-Joulin S, Mistretta F, et al. Evaluation of several ultrasonography scoring systems for synovitis and comparison to clinical examination: results from a prospective multicentre study of rheumatoid arthritis. *Ann Rheum Dis.* 2010;69:828-833.
42. Wakefield RJ, D'Agostino MA, Naredo E, et al. After treat-to-target: can a targeted ultrasound initiative improve RA outcomes? *Ann Rheum Dis.* 2012;71:799-803.

8 Dual energy X-ray absorptiometry in rheumatoid arthritis

Atul Deodhar

Introduction

Bone damage in rheumatoid arthritis (RA) has three distinct phenotypes: marginal erosions in the affected joints, periarticular osteoporosis, and generalized osteoporosis [1]. While systemic inflammation is the main effector mechanism causing generalized osteoporosis, physical inactivity and corticosteroid use may also play a role in the pathogenesis. Local inflammation in the vicinity of joints, along with reduced mechanical loading, is important in the development of periarticular osteoporosis, whereas invading synovial pannus leads to focal marginal erosions, the radiographic hallmark of RA [2]. Experiments on knockout mice have shown that the osteoclasts are the only cell types that are capable of causing all three types of bone damage [3].

Bone remodeling in rheumatoid arthritis

Normal bone remodeling is an orderly ‘coupled’ process with osteoclasts starting the resorption of the bone matrix and the osteoblasts depositing new lamellar bone (Figure 8.1) [4]. It is known that rheumatoid pathology leads to a bone-remodeling imbalance by increasing bone resorption and suppressing bone formation. The pro-inflammatory cytokines in the rheumatoid synovium lead to expression of receptor activator of nuclear factor $\kappa\beta$ ligand (RANKL) on immune cells as well as increased levels of dickkopf-1 (DKK-1). The receptor activator of nuclear factor $\kappa\beta$ (RANK)-RANKL interaction is important for osteoclast development and

activation, while DKK-1 suppresses bone formation by osteoblasts by inhibiting the Wnt signaling pathway [5]. Figure 8.2 shows the role of the immune system in the pathogenesis of bone damage in RA [6]. The marginal erosions are developed by both an ‘outside in’ and an ‘inside out’ process (bone damage caused by osteoclasts developed from the monocyte-macrophage lineage in the synovial membrane and from the bone marrow, respectively) [7]. In contrast, periarticular, as well as generalized, osteoporosis seen in RA is a process led by bone marrow-derived osteoclasts [8].

Bone damage imaging in rheumatoid arthritis

Several imaging modalities are used to assess bone damage in RA (Figure 8.3) [9]. Scoring plain radiographs for joint space narrowing and erosions (eg, Sharp score and its modifications, Larsen score) have long been the gold standard for assessing and monitoring joint damage in RA [10]. Magnetic resonance imaging (MRI) scanning of hands has emerged as a more sensitive and specific tool to assess the erosions. As seen in Chapter 6, MRI scan of the hands can assess bone marrow edema, a precursor of erosions, as well as synovial proliferation [11]. Despite these distinct advantages, MRI cannot assess periarticular or generalized osteoporosis in RA.

Dual energy X-ray absorptiometry

Periarticular osteoporosis is the first radiographic sign in RA, even before the development of joint space narrowing and erosions. Thus, assessing periarticular osteoporosis has the advantage of measuring disease-related bone damage in the earliest stages of RA [12]. To objectively assess periarticular osteoporosis, hand bone density measurement can be done directly using dual energy X-ray absorptiometry (DXA) or indirectly by digital X-ray radiogrammetry (DXR).

Initial studies on hand bone density measurement using DXA required modifying the existing protocols of lumbar spine DXA measurements [12]. Early studies included the entire hand (plus the carpal bones) for measurement, but in subsequent studies, limited

measurements of juxta-articular osteoporosis in the distal (1.5 cm) of the metacarpal bones were also shown to have good reproducibility (Figures 8.4 and 8.5) [12–14]. If the area of the entire hand is included in the measurement, then bone mineral content (BMC) is preferred over bone mineral density (BMD) because BMC does not depend on the area of measurement. This is especially true in patients with RA, where disease-related deformities could affect the hand area (Figure 8.6) [12].

Earlier studies showed that males have higher hand BMC than females, and patients with RA have lower hand BMC compared to age and sex-matched controls (Figure 8.7) [12]. Hand BMD correlated with the lumbar spine and femoral neck BMD, body size (height and weight), grip strength, and inversely with erythrocyte sedimentation rate (ESR) and X-ray scores (Figure 8.8) [13,14]. The rate of hand bone loss was highest in patients with early RA (disease duration less than 2 years) treated with nonbiologic disease-modifying antirheumatic drugs (DMARDs) despite clinical improvement and correlated with baseline C-reactive protein (CRP) levels (Figure 8.9) [15].

As previously noted, because periarticular osteoporosis is the earliest sign of RA in hands (even before the development of joint space narrowing or erosions), there is interest in investigating if a change in hand BMC would be a prognostic marker of hand function. A prospective observational study showed that percent change in hand BMC over 5 years did indeed correlate with measures of physical function (eg, 36-item Short Form Health Survey [SF-36], Duruoz hand function index, health assessment questionnaire score [HAQ]) at 5 years, and a loss of >1.17 g in the first 6 months predicted a poor hand functional outcome at 5 years (odds ratio=6.9) (Figure 8.10) [16].

Hand BMD measurement may also have diagnostic significance in early undifferentiated arthritis. In a 12-month prospective study on patients with early undifferentiated arthritis, patients who subsequently were diagnosed as having RA lost significantly more bone mass compared to those who either did not have inflammatory arthritis or had a non-rheumatoid inflammatory arthritis on follow-up [17]. Mean CRP level and rheumatoid factor were

independent predictors of the hand BMD loss [17]. In another study, hand DXA was found to be more sensitive than radiographs for measuring disease-related bone damage in patients with early RA (in this study, disease duration less than 12 months) [18].

Bone densitometry measurement by digital X-ray radiogrammetry

DXR, a computer-aided technique for the measurement of cortical BMD of metacarpal bones using digitized hand X-ray, is another technique to assess hand bone density (Figures 8.11 and 8.12) [20]. DXR determines:

- BMD (g/cm^2);
- cortical thickness (cm);
- metacarpal bone width (cm);
- metacarpal index (based on mean cortical thickness normalized for the mean outer bone diameter of the metacarpal bones); and
- porosity index (correction factor of DXR–BMD) [21].

Several investigators have used DXR for assessing progression of the disease and hand function in RA. For example, in a 10-year longitudinal study, absolute hand DXR–BMD loss at 1 year was an independent predictor of radiographic outcome at 5 and 10 years. The odds ratio for radiographic progression was 3.5 at 10 years among patients with hand BMD loss [22]. The association between mortality and DXR–BMD in patients with RA was evaluated in a retrospective analysis over a 30-year period. The DXR–BMD on baseline X-rays, along with Steinbrocker functional class III or IV, the physician’s global assessment, and ESR were significant predictors of mortality [23].

Qualitative ultrasound

Quantitative ultrasound (QUS) is a third technique to measure bone density, although it is less sensitive than DXR in quantifying bone loss. Figure 8.13 shows a comparison of the DXR technique with QUS for the severity-dependent quantification of bone loss based on the Larsen score [20]. The DXR–BMD revealed a significant reduction (25%), whereas the QUS parameters (measured at the radius and phalanx) failed to show a significant reduction [20].

Taken together, the studies described above show that hand bone densitometry by DXA or DXR can offer additional information over erosion counts and inflammatory markers in

outcome studies in RA. Compared to an MRI, bone densitometry is cheaper and the equipment required is more easily available. Bone density measurement in RA, therefore, can be used for assessing disease activity (process measure), as well as for predicting outcome.

Bone density measurement for generalized osteoporosis in rheumatoid arthritis

Generalized osteoporosis is the third type of bone damage seen in patients with RA. In fact, RA is an important enough risk factor for osteoporosis that it is added in the fracture assessment tool (FRAX). Compared to age- and sex-matched controls, prevalence of osteoporosis in patients with RA increases two-fold [24]. Hip and spine bone density measurements in patients with early RA showed high bone loss at the lumbar spine (–2.4 %) and at the hip (–4.3 %); this loss was higher in patients with active disease (measured by CRP) and worse function (measured by HAQ) [25]. However, when looking at generalized osteoporosis in patients with RA, it is important to remember that fracture is the most clinically relevant outcome. The large General Practice Research Database cohort study showed that when compared with healthy controls, the risk of osteoporotic fractures in patients with RA is increased 1.5-fold [26].

Treatment of bone loss in rheumatoid arthritis

With the advent of biologics to treat rheumatoid arthritis, all three types of bone damage have become treatable. Anti-TNF treatment can arrest loss of BMD at the spine and the hip [27]. In the BEST study, all four groups of patients with aggressively treated early RA, showed only moderate generalized bone loss at 2 years at the hip and spine (–0.5% to 1.0%) and patients in remission had less bone loss compared to those not in remission [28]. These results indicate that adequate suppression of inflammation is essential for prevention of generalized bone loss in RA. In a Phase III double-blind randomized placebo-controlled pivotal trial, adalimumab was able to halt progression of hand erosion, but hand bone loss (measured by DXR) was inadequately suppressed [29]. The authors, therefore, concluded that quantitative measurement of osteoporosis may be a more sensitive tool for assessment of inflammatory bone damage in RA [30]. Denosumab, a fully human monoclonal antibody against RANKL, recently showed suppression of bone loss in hand, lumbar spine, and hip (measured by DXA; Figure 8.14), and arrested erosions in patients with RA [29,31].

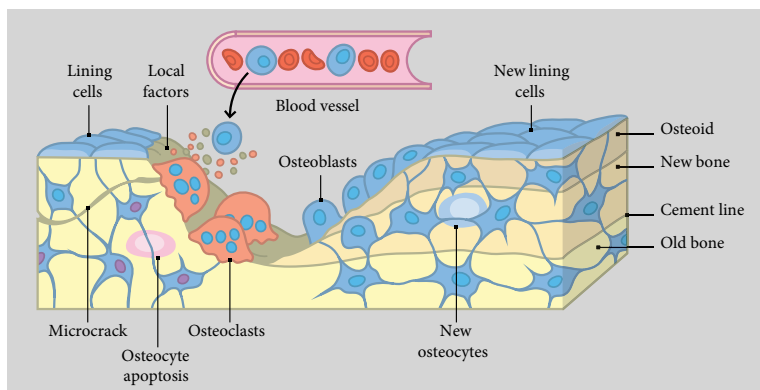


Figure 8.1 Normal bone remodeling involved in repairing a microcrack. Microcracks sever osteocyte canaliculi, leading to osteocytic apoptosis. This damage signals lining cells and causes osteocytes to release local factors that attract osteoclast precursors from blood and marrow into the remodeling compartment. Osteoclasts resorb the bone matrix and the microcrack, and then osteoblasts deposit new lamellar bone. Reproduced with permission from Seeman and Delmas [4] ©NEJM.

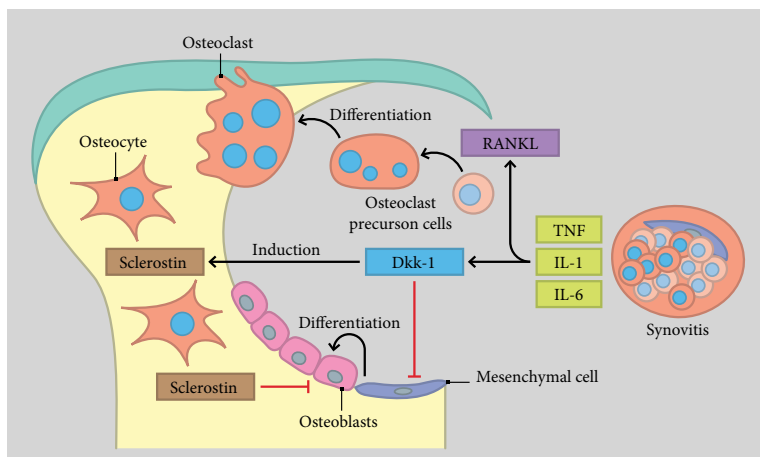


Figure 8.2 Stimulation of osteoclasts and suppression of osteoblasts leads to altered bone remodeling in rheumatoid arthritis. The pro-inflammatory cytokines (TNF- α , IL-1, IL-6) released by immune cells in the rheumatoid synovium stimulate expression of receptor activator of nuclear factor κ B ligand (RANKL) on cells including synovial fibroblasts, T cells, and osteoblasts. RANKL interacts with the receptor activator of nuclear factor κ B (RANK), expressed on osteoclast precursors and osteoclasts, leading to osteoclast development and activation [2]. The cytokines also lead to secretion of DKK-1, a potent suppressor of osteoblasts by inhibiting the Wnt signaling pathway directly and through stimulation of sclerostin [5]. DKK-1, dickkopf-related protein 1; IL, interleukin; TNF, tumor necrosis factor. Reproduced with permission from Schett and Gravallesse [6] ©Macmillan Publishers Limited.

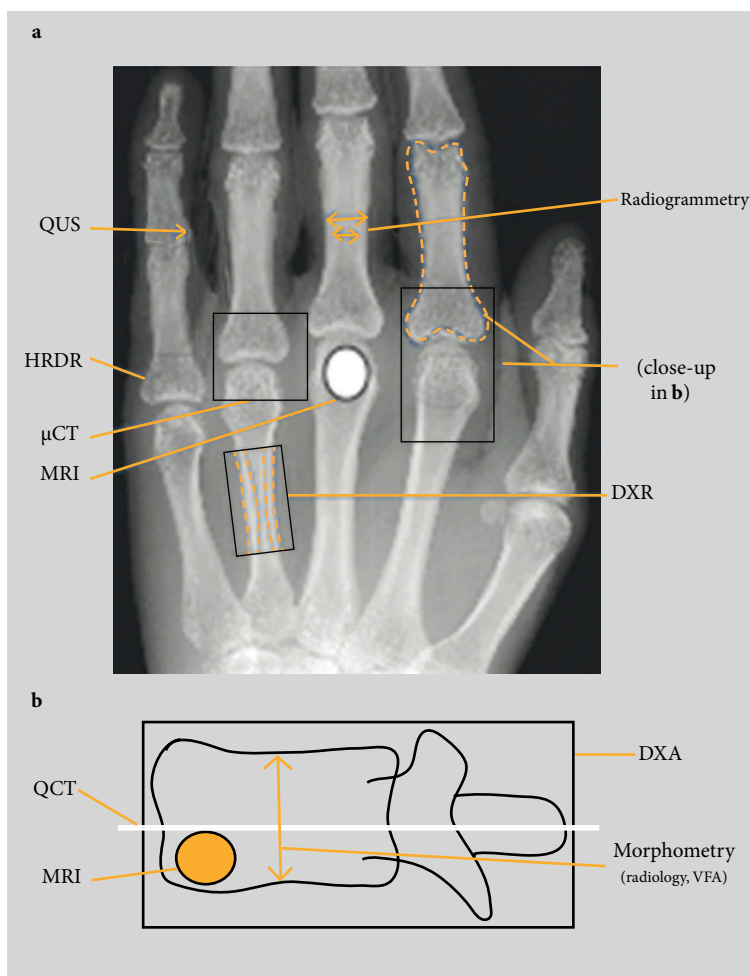


Figure 8.3 Imaging modalities used to assess bone damage in the hands and vertebra in rheumatoid arthritis. X-rays are traditionally considered to be the 'gold-standard' to assess bone damage in rheumatoid arthritis. However, there are several other modalities, as shown in **a** and **b**. DXA, dual-energy X-ray absorptiometry; DXR, digitalized radiogrammetry; HRDR, high-resolution digital radiography; μ CT, micro-computed tomography; MRI, magnetic resonance imaging; QCT, quantitative computer tomography; QUS, quantitative ultrasound; VFA, vertebral fracture assessment. Reproduced with permission from Geusens and Lems [9] ©BMC.



Figure 8.4 Hand bone densitometry using dual energy X-ray absorptiometry. The image shows the area selected for analysis, excluding the distal radius and ulna but including the entire hand plus the carpal bones. The results of dual energy X-ray absorptiometry are expressed as the projected area (cm^2), bone mineral content (BMC; g), and the areal bone mineral density (BMD; g/cm^2). Reproduced with permission from Peel et al [13] ©Wiley.

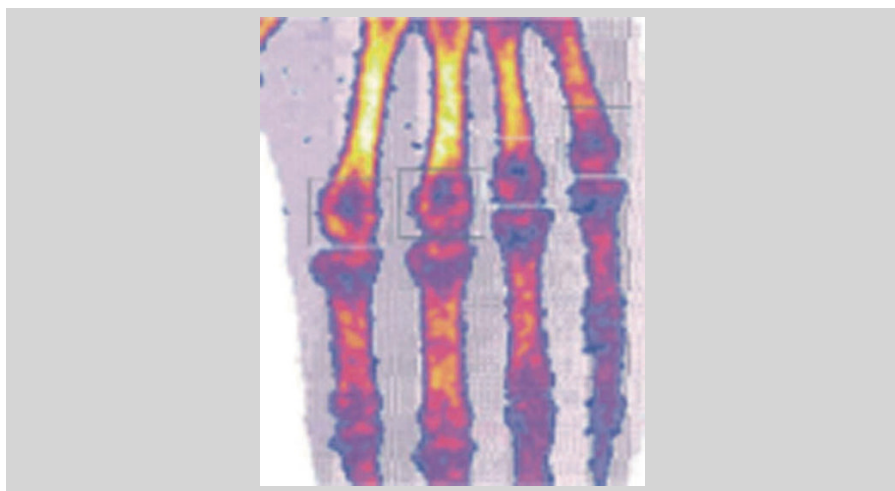


Figure 8.5 Hand bone densitometry by dual energy X-ray absorptiometry: measurement of metacarpal heads. The image shows measurement of hand bone mineral density using a limited area selected for analysis. Rather than choosing the entire hand, the juxta-articular distal (1.5 cm) of the metacarpal bones are included in this analysis. This method had 1.6% coefficient of variation for duplicate measurements. Reproduced with permission from Jensen et al [14] ©BMJ.

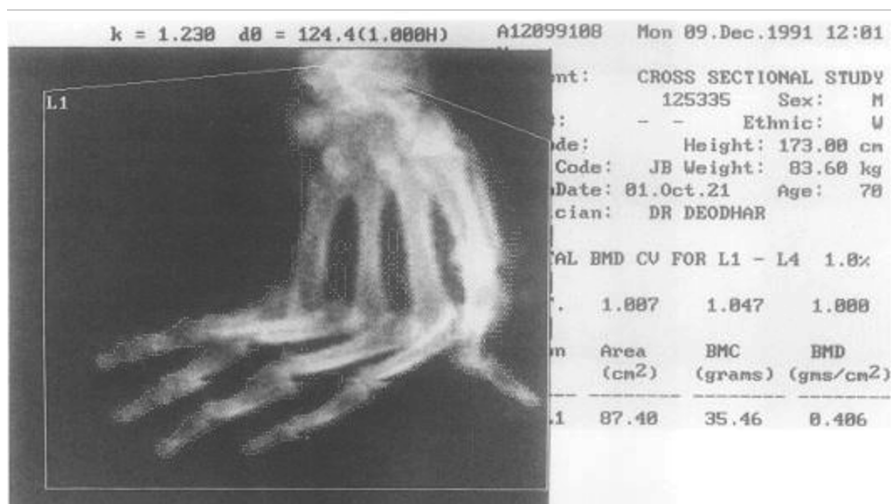


Figure 8.6 Hand bone densitometry by dual-energy X-ray absorptiometry in a patient with severe hand deformities due to rheumatoid arthritis. Patients with rheumatoid arthritis have lower hand bone mineral content (BMC) compared to age- and sex-matched controls. Because the hand surface area can change due to progressive hand deformities, BMC (rather than bone mineral density [BMD], which depends upon the area) should be monitored. BMC is independent of surface area. Reproduced with permission from Deodhar et al [12] ©BMJ.

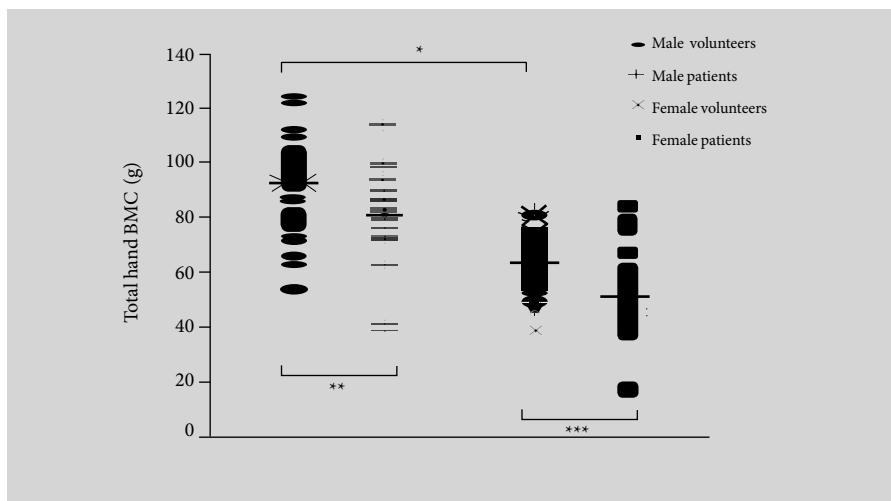


Figure 8.7 Hand bone mineral content in controls and patients with rheumatoid arthritis. This graph shows the total hand bone mineral content (BMC; g) in normal volunteers (male and female) and patients with rheumatoid arthritis (RA). After correcting for body size, male volunteers had significantly higher BMC than female volunteers, and patients with RA had significantly lower hand BMC than age- and sex-matched volunteers. * $P=0.01$; ** $P=0.005$; *** $P<0.005$. Reproduced with permission from Deodhar et al [12] ©BMJ.

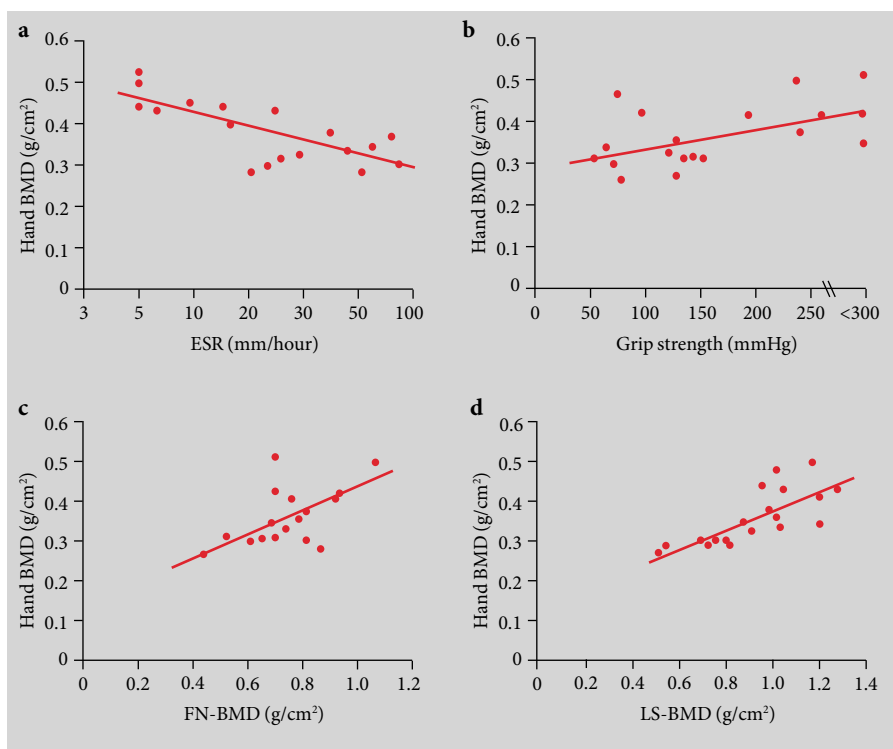


Figure 8.8 Hand bone mineral density correlations in patients with early rheumatoid arthritis. The graphs show the relationship between hand bone mineral density (BMD) and markers of disease activity in 20 patients with early rheumatoid arthritis: (a) erythrocyte sedimentation rate (ESR; $r=-0.81$; $P<0.0001$); (b) function/grip strength ($r=0.49$; $P=0.03$); (c) BMD of the femoral neck (FN; $r=0.67$; $P=0.002$); (d) BMD of the lumbar spine (LS; $r=0.72$; $P=0.0003$). Reproduced with permission from Peel et al [13] ©Wiley.

Study entry



12 months



Figure 8.9 Loss of hand bone mineral content over 1 year in a patient with rheumatoid arthritis treated with nonbiologic disease-modifying antirheumatic drugs (DMARDs). Despite showing clinical improvement in the number of tender joints, swollen joints, erythrocyte sedimentation rate, and grip strength, this person lost 4.6 g (9.6%) hand bone mineral content over a one-year period. This indicates that nonbiologic disease-modifying antirheumatic drugs may not be able to arrest hand bone loss. Reproduced with permission from Deodhar et al [12] ©Wiley.

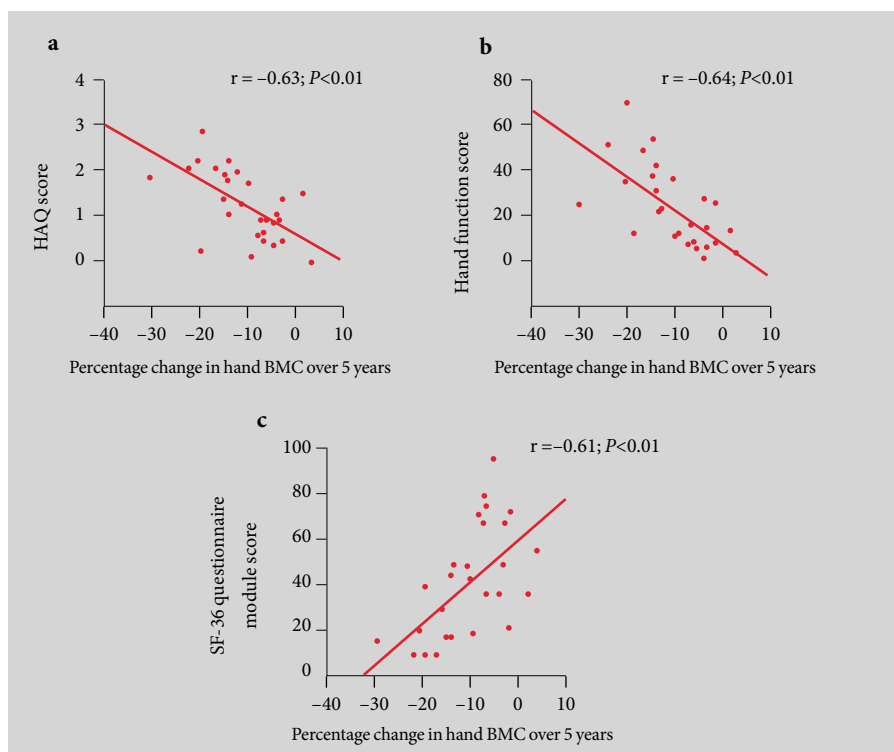


Figure 8.10 Correlation between cumulative loss of hand bone mineral content over 5 years and other outcome measures in patients with early rheumatoid arthritis. The percent change in hand bone mineral content (BMC) over 5 years correlated with (a) health assessment questionnaire (HAQ) score; (b) Duruoz hand function index; and inversely with (c) physical function, as measured by Short Form (SF-36) Health Survey physical function module score. Change in hand BMC was found to be a prognostic marker, as a BMC loss of >1.17 g in the first 6 months predicted a poor hand functional outcome at 5 years, with an odds ratio of 6.9. Reproduced with permission from Deodhar et al [16] ©BMJ.



Figure 8.11 Hand bone density measurement by digital X-ray radiogrammetry. Radiographs are scanned into a digital X-ray radiogrammetry (DXR) system (a). (b) Screen view of DXR with the marked region of interest positioned at the metacarpal diaphysis II-IV (see Figure 8.12 for a close-up). (c) Screen view of the scanning protocol. The coefficient of variation (CV) of DXR measurements in the hands of premenopausal women was 0.68% and 0.61% in postmenopausal women [19]. Reproduced with permission from Pfeil et al [20] ©Wiley.



Figure 8.12 Digital X-ray radiogrammetry. A scanned and processed hand radiograph with the three regions of interest. The digitized image is subjected to a number of image processing algorithms where the three regions of interests around the narrowest part of the second, third, and fourth metacarpal joints are automatically identified. (Close up of 'B' from Figure 8.11). Reproduced with permission from Pfeil et al [20] ©Wiley.

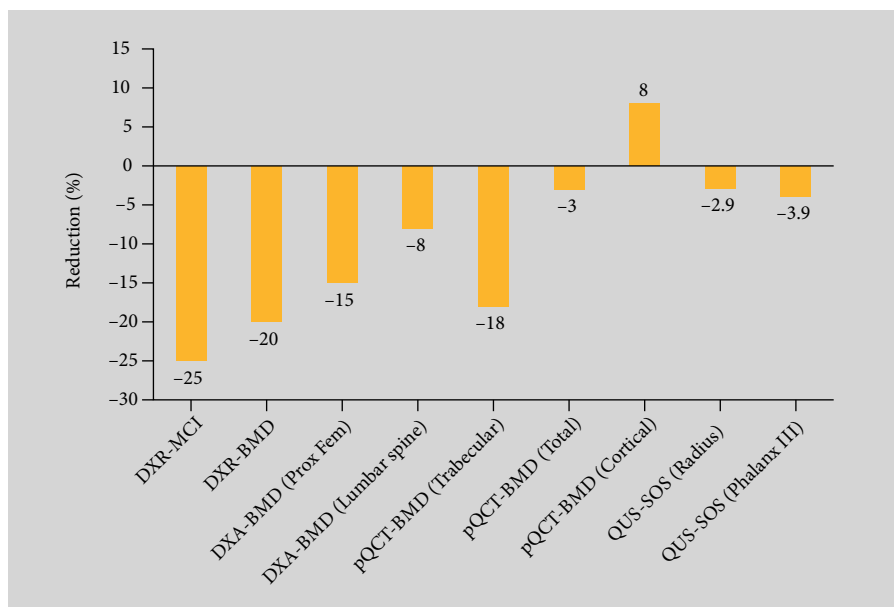


Figure 8.13 Severity-dependent bone loss of different evaluated osteodensitometric methods between a Larsen score of 1 and 5. BMD, bone mineral density; DXR, digital X-ray radiogrammetry; DXA, dual energy X-ray absorptiometry; MCI, metacarpal index; pQCT, peripheral quantitative computed tomography; QUS, quantitative ultrasound; SOS, speed of sound. Reproduced with permission from Pfeil et al [20] ©Wiley.

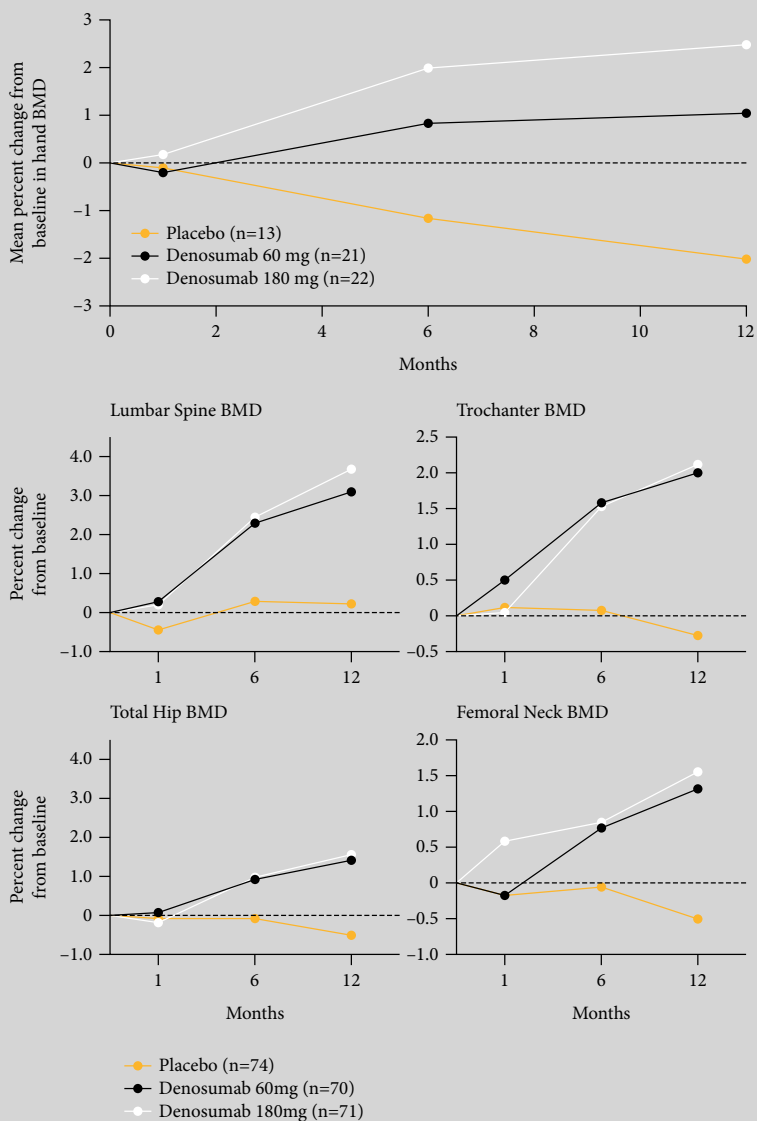


Figure 8.14 Denosumab reverses bone loss (as measured by dual energy X-ray absorptiometry) in hands, lumbar spine, and femoral neck in patients with rheumatoid arthritis. Denosumab, an anti-receptor activator of nuclear factor κ B ligand monoclonal antibody, inhibits periarticular and systemic bone loss in hand, lumbar spine, and hip in patients with rheumatoid arthritis. BMD, bone mineral density. Adapted with permission from Deodhar et al [29] and Dore et al [31].

References

1. Deodhar AA, Woolf AD. Bone mass measurement and bone metabolism in rheumatoid arthritis: a review. *Br J Rheumatol*. 1996;35:309-322.
2. Schett G, Gravallese E. Bone erosion in rheumatoid arthritis: mechanisms, diagnosis and treatment. *Nat Rev Rheumatol*. 2012;8:656-664.
3. Gravallese EM, Harada Y, Wang JT, Gorn AH, Thornhill TS, Goldring SR. Identification of cell types responsible for bone resorption in rheumatoid arthritis and juvenile rheumatoid arthritis. *Am J Pathol*. 1998;152:943-951.
4. Seeman E, Delmas PD. Bone quality – the material and structural basis of bone strength and fragility. *N Engl J Med*. 2006;354:2250-2261.
5. Diarra D, Stolina M, Polzer K, et al. Dickkopf-1 is a master regulator of joint remodeling. *Nat Med*. 2007;13:156-163.
6. Schett G, Gravallese E. Bone erosion in rheumatoid arthritis: mechanisms, diagnosis and treatment. *Nat Rev Rheumatol*. 2012;8:656-664.
7. Schett G, Firestein GS. Mr Outside and Mr Inside: classic and alternative views on the pathogenesis of rheumatoid arthritis. *Ann Rheum Dis*. 2010;69:787-789.
8. Goldring SR. Periarticular bone changes in rheumatoid arthritis: pathophysiological implications and clinical utility. *Ann Rheum Dis*. 2009;68:297-299.
9. Geusens P, Lems WF. Osteoimmunology and osteoporosis. *Arthritis Res Ther*. 2011;13:242.
10. Brower AC. Use of the radiograph to measure the course of rheumatoid arthritis. The gold standard versus fool's gold. *Arthritis Rheum*. 1990;33:316-324.
11. Cohen SB, Potter H, Deodhar A, Emery P, Conaghan P, Ostergaard M. Extremity magnetic resonance imaging in rheumatoid arthritis: Updated literature review. *Arthritis Care Res (Hoboken)*. 2011;63:660-665.
12. Deodhar AA, Brabyn J, Jones PW, Davis MJ, Woolf AD. Measurement of hand bone mineral content by dual energy X-ray absorptiometry: development of the method, and its application in normal volunteers and in patients with rheumatoid arthritis. *Ann Rheum Dis*. 1994;53:685-690.
13. Peel NF, Spittlehouse AJ, Bax DE, Eastell R. Bone mineral density of the hand in rheumatoid arthritis. *Arthritis Rheum*. 1994;37:983-991.
14. Jensen T, Klarlund M, Hansen M, et al; TIRA Group. Bone loss in unclassified polyarthritis and early rheumatoid arthritis is better detected by digital x ray radiogrammetry than dual x ray absorptiometry: relationship with disease activity and radiographic outcome. *Ann Rheum Dis*. 2004;63:15-22.
15. Deodhar AA, Brabyn J, Jones PW, Davis MJ, Woolf AD. Longitudinal study of hand bone densitometry in rheumatoid arthritis. *Arthritis Rheum*. 1995;38:1204-1210.
16. Deodhar AA, Brabyn J, Pande I, Scott DL, Woolf AD. Hand bone densitometry in rheumatoid arthritis, a five year longitudinal study: an outcome measure and a prognostic marker. *Ann Rheum Dis*. 2003;62:767-770.
17. Haugeberg G, Green MJ, Quinn MA, et al. Hand bone loss in early undifferentiated arthritis: evaluating bone mineral density loss before the development of rheumatoid arthritis. *Ann Rheum Dis*. 2006;65:736-740.
18. Haugeberg G, Green MJ, Conaghan PG, et al. Hand bone densitometry: a more sensitive standard for the assessment of early bone damage in rheumatoid arthritis. *Ann Rheum Dis*. 2007;66:1513-1517.
19. Jorgensen JT, Andersen PB, Rosholm A, Bjarnason NH. Digital X-ray radiogrammetry: a new appendicular bone densitometric method with high precision. *Clin Physiol*. 2000;20:330-335.
20. Pfeil A, Haugeberg G, Hansch A, et al. Value of digital X-ray radiogrammetry in the assessment of inflammatory bone loss in rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2011;63:666-674.
21. Rosholm A, Hyldstrup L, Backgaard L, Grunkin M, Thodberg HH. Estimation of bone mineral density by digital X-ray radiogrammetry: theoretical background and clinical testing. *Osteoporos Int*. 2001;12:961-969.
22. Hoff M, Haugeberg G, Odegard S, et al. Cortical hand bone loss after 1 year in early rheumatoid arthritis predicts radiographic hand joint damage at 5-year and 10-year follow-up. *Ann Rheum Dis*. 2009;68:324-329.
23. Book C, Algulini J, Nilsson JA, Saxne T, Jacobsson L. Bone mineral density in the hand as a predictor for mortality in patients with rheumatoid arthritis. *Rheumatology*. 2009;48:1088-1091.

24. Haugeberg G, Uhlig T, Falch JA, Halse JI, Kvien TK. Bone mineral density and frequency of osteoporosis in female patients with rheumatoid arthritis: results from 394 patients in the Oslo County Rheumatoid Arthritis register. *Arthritis Rheum.* 2000;43:522-530.
25. Gough AK, Lilley J, Eyre S, Holder RL, Emery P. Generalised bone loss in patients with early rheumatoid arthritis. *Lancet.* 1994;344:23-27.
26. van Staa TP, Geusens P, Bijlsma JW, Leufkens HG, Cooper C. Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. *Arthritis Rheum.* 2006;54:3104-3112.
27. Vis M, Havaardsholm EA, Haugeberg G, et al. Evaluation of bone mineral density, bone metabolism, osteoprotegerin and receptor activator of the NFkappaB ligand serum levels during treatment with infliximab in patients with rheumatoid arthritis. *Ann Rheum Dis.* 2006;65:1495-1499.
28. Guler-Yuksel M, Allaart CF, Goekoop-Ruiterman YP, et al. Changes in hand and generalised bone mineral density in patients with recent-onset rheumatoid arthritis. *Ann Rheum Dis.* 2009;68:330-336.
29. Deodhar A, Dore RK, Mandel D, et al. Denosumab-mediated increase in hand bone mineral density associated with decreased progression of bone erosion in rheumatoid arthritis patients. *Arthritis Care Res (Hoboken).* 2010;62:569-574.
30. Hoff M, Kvien TK, Kalvesten J, Elden A, Haugeberg G. Adalimumab therapy reduces hand bone loss in early rheumatoid arthritis: explorative analyses from the PREMIER study. *Ann Rheum Dis.* 2009;68:1171-1176.
31. Dore RK, Cohen SB, Lane NE, et al; Denosumab RA Study Group. Effects of denosumab on bone mineral density and bone turnover in patients with rheumatoid arthritis receiving concurrent glucocorticoids or bisphosphonates. *Ann Rheum Dis.* 2010;69:872-875.

PART THREE

Treatment of rheumatoid arthritis

9 Methotrexate

David Sandoval and Graciela Alarcón

Introduction

Methotrexate is an antimetabolite agent that is very similar in structure to folic acid (folic acid analogue)[1]. Aminopterin, another folic acid analogue and a methotrexate precursor, was used first for the treatment of rheumatoid arthritis (RA) and psoriasis by Gubner and Ginsberg in 1951 [2]. Methotrexate was initially more popular in the field of dermatology than in rheumatology. In 1964, Black published a double-blind study in psoriatic arthritis [3], which was followed by the pioneering work of Hoffmeister and the discovery that methotrexate is useful in the treatment of RA [4]. However, it was not until the 1980s that methotrexate became the standard care for RA due to the results of four double-blind randomized clinical trials [5–8]. These studies led Wilkens in 1990 to suggest that methotrexate should be used in all patients with RA as a second-line treatment after non-steroidal anti-inflammatory drugs (NSAIDs) [9]. In this chapter, we will discuss historical aspects related to methotrexate, its mechanisms of action, pharmacokinetics, dosing, its potential benefits in the treatment of RA, monitoring administration, and managing potential side effects.

Historical perspective

When aminopterin was first introduced by Gubner and Ginsberg in 1951 as a potential treatment option for RA [2], corticosteroids were thought to ‘cure’ RA; thus, methotrexate did not come to the forefront for the treatment of RA until much later when four pivotal double-blind controlled trials

prompted its approval for the treatment of RA by the US Food and Drug Administration (FDA) in 1988 [10,11].

Methotrexate is a chemotherapeutic agent and is presently used in the treatment of certain cancers. It is also used as an abortive agent. As shown in Figure 9.1, the role of methotrexate for the treatment of RA has evolved over the years.

Mechanism of action and pharmacokinetics

Methotrexate contains an amino group (NH_2), a methyl group (CH_3), and a fully-oxidized pteridine ring, which renders the molecule inactive as a cofactor (Figure 9.2) [12]. The similar structure of dihydrofolic acid (Figure 9.3) and methotrexate suggests that methotrexate is a competitive inhibitor of folic acid [13]. Figure 9.4 represents the main mechanisms of action of methotrexate in different cell compartments [13].

Methotrexate exerts several blocking actions over the folate metabolic pathways. The most cited mechanism is the inhibition of dihydrofolic reductase (DHFR). Extracellular methotrexate is brought into the cell by α and β folate receptors. Once inside the cell, methotrexate and 7-OH-methotrexate are metabolized to polyglutamates (methotrexate-glu). Methotrexate-glu binds to DHFR and has high affinity for enzymes that require folate as cofactors, including thymidylate synthase (TS) and 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) tranformylase [13]. The inhibition of TS interferes with the synthesis of DNA. The increase of AICAR leads to the release of adenosine into the blood stream [14,15].

Once administered, 3–12% of the methotrexate molecules are hydroxylated in the liver and circulate as 7-OH-methotrexate. Extracellular methotrexate is attached to α and β folate receptors. A number of anti-inflammatory effects exerted by methotrexate seem to be related to the increased levels of extracellular adenosine, which in turn produce an inhibitory effect on interleukin (IL)-8 in peripheral blood mononuclear cells (PBMC), a reduction of IL-6, and a decreased expression of synovial collagenase. Other well-known effects of methotrexate include (Table 9.1):

- decreased IL-1 activity [16];
- decreased levels of IL-6 and soluble IL-2 after 12 weeks of therapy [17]; and
- decreased production of leukotriene B₄ [18].

The effects of methotrexate at the synovial tissue level include:

- reduction of monocyte cell growth and induction of their apoptosis [19];
- increased expression of IL-4 and IL-10 genes and decrease expression of pro-inflammatory Th1 cytokines genes (IL-2 and interferon- γ) [13];
- indirect inhibition of cyclooxygenase-2 (COX-2) synthesis and neutrophil chemotaxis [13]; and
- indirect inhibitory effects on synovial metalloproteinase production and stimulatory effect on their inhibitors (tissue inhibitor of metalloproteinases) [13].

Methotrexate can be given orally or parenterally. When administered orally, the absorption is dose-dependent. Peak serum levels are achieved within 1–2 hours. With doses of up to 25 mg, the bioavailability is about 60%; at higher doses, methotrexate is not absorbed as well. With subcutaneous administration, peak levels are reached in 1 hour. After absorption, about 50% of methotrexate binds to albumin [20].

Methotrexate is excreted mainly by the kidneys (about 70–80%) and the biliary tract (about 10–20%). Renal excretion is through glomerular filtration and tubular secretion. The toxicity of methotrexate is related primarily to its clearance rate by the kidney, rather than to the peak level achieved after its administration [21]. Some interactions of methotrexate with other drugs have been documented. Table 9.2 lists these potential interactions.

Dosing

Methotrexate is available in tablet and injectable form. The oral form consists of 2.5 mg tablets. The most common injectable form is 25 mg/mL. Table 9.3 shows the common routes of administration and dosing.

In chronic liver disease and chronic kidney disease, the drug should be monitored closely and it is recommended to adjust the dose (Table 9.4). Patients with end-stage renal disease (ESRD) on hemodialysis should not be treated with methotrexate [26].

Benefits

The response rate to methotrexate treatment is approximately 70%; response is generally observed after 6–8 weeks of therapy [27]. This efficacy rate has been corroborated in multiple

studies [28–30]. The drug-survival curve of methotrexate indicates that at 5 years, there is a 50% probability of still taking the drug, compared to 15–20% for other drugs (eg, gold salts, D-penicillamine) [1]. Table 9.5 shows a comparison of efficacy rates of the most common oral DMARDs for the treatment of RA [27].

Radiographic progression seems to continue in patients on methotrexate but at a slower rate. Figure 9.5 shows a summary of studies of radiographic progression with methotrexate (includes a study in which methotrexate and etanercept are compared) [31]. There is strong evidence suggesting that the combination of methotrexate and biologic agents is superior to methotrexate alone in the prevention of radiographic progression (Figure 9.6) [32].

Monitoring

Table 9.6 shows the accepted recommendations for monitoring methotrexate treatment [32–34]; these recommendations were originally established in 1994. In addition, the following should be taken into consideration:

- age and cumulative dose predispose to liver toxicity;
- pulmonary injury may occur at any time;
- monitor for infections and the possible occurrence of lymphomas; and
- take caution with the concomitant administration of other antifolates.

The threshold to recommend a liver biopsy by rheumatologists has increased over the years, which is in conflict with what dermatologists recommend [35]. In other words, patients on methotrexate who are treated by dermatologists may undergo liver biopsies more frequently than those treated by rheumatologists. For these patients, it seems reasonable to consider liver biopsies when risk factors are present, including history of diabetes, hepatitis, obesity and alcohol consumption [36].

Special populations

In certain populations, special care should be taken with methotrexate treatment.

- **Pregnancy and lactation:** methotrexate is in Category X as per the FDA classification (ie, should not be taken). During lactation, methotrexate is contraindicated [37].
- **Female fertility:** methotrexate has a temporary negative effect on fertility; however, 97% of women conceived one year after methotrexate discontinuation [37]. Women pursuing

pregnancy should discontinue methotrexate at least 3, but preferably 6, months before planning a pregnancy [37,38].

- **Male fertility:** methotrexate produces marginal reversible oligospermia [37]. Men pursuing fathering a child should discontinue methotrexate 6 months before planning a pregnancy [37].
- **Children:** same as adults, although less frequent monitoring is probably reasonable [39].
- **Elderly:** American College of Rheumatology (ACR) guidelines are the same in the elderly as for younger adults [40]. Renal function should be monitored.

Side effects

Table 9.7 shows the reported adverse events with low-dose methotrexate therapy [33]. Methotrexate nodulosis has been well described in patients receiving methotrexate for RA, but not for other conditions [24]. Figure 9.7 is a chest computerized tomography (CT) scan of a patient with non-specific interstitial pneumonitis pattern after 3 months of therapy with methotrexate for RA. The patient had a normal chest X-ray film prior to initiation of methotrexate therapy. Figure 9.8 is an image of a patient who developed oral ulcers shortly after the initiation of treatment with methotrexate without concomitant folic acid administration.

Management of side effects

Figure 9.9 depicts an accepted general algorithm for initial management of suspected adverse events related to methotrexate treatment for RA. Table 9.8 summarizes the usual recommendations for the management of side effects related to methotrexate administration for the treatment of RA [41–47]. Table 9.9 summarizes some of the general accepted recommendations for special circumstances [41,47,49–53]. In addition, it is highly recommended that the rheumatologist discusses the specific situation with the surgeon involved in patient care [48].

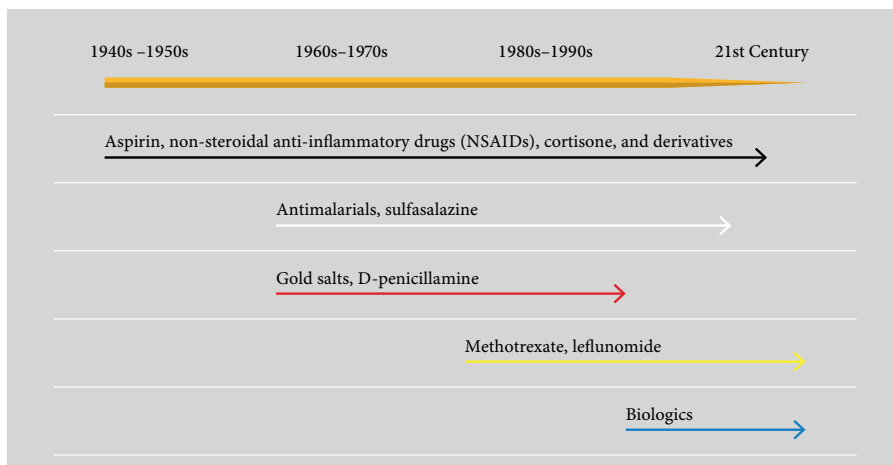


Figure 9.1 Evolution of rheumatoid arthritis treatment over time.

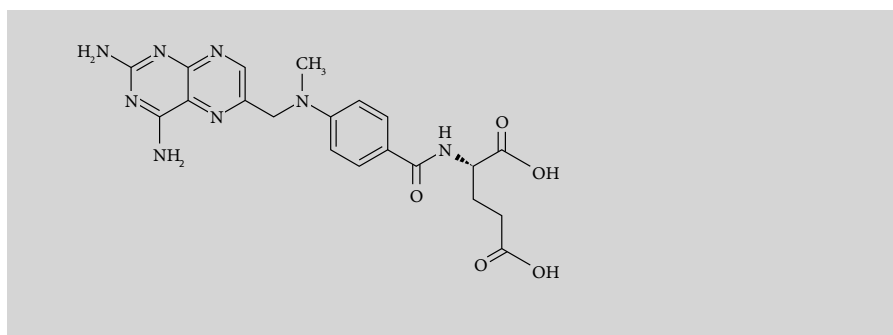


Figure 9.2 Molecular structure of methotrexate.

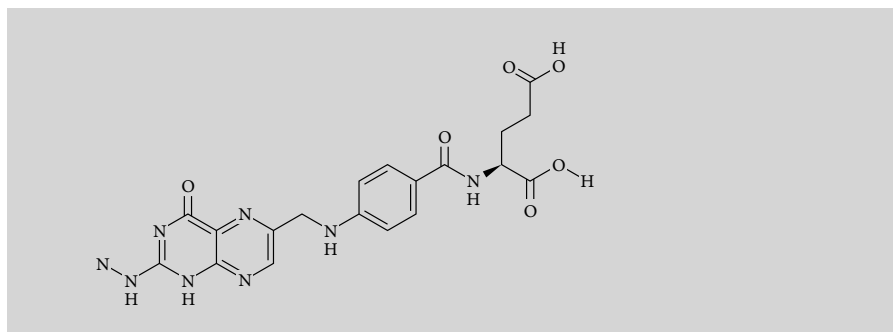


Figure 9.3 Molecular structure of dihydrofolic acid.

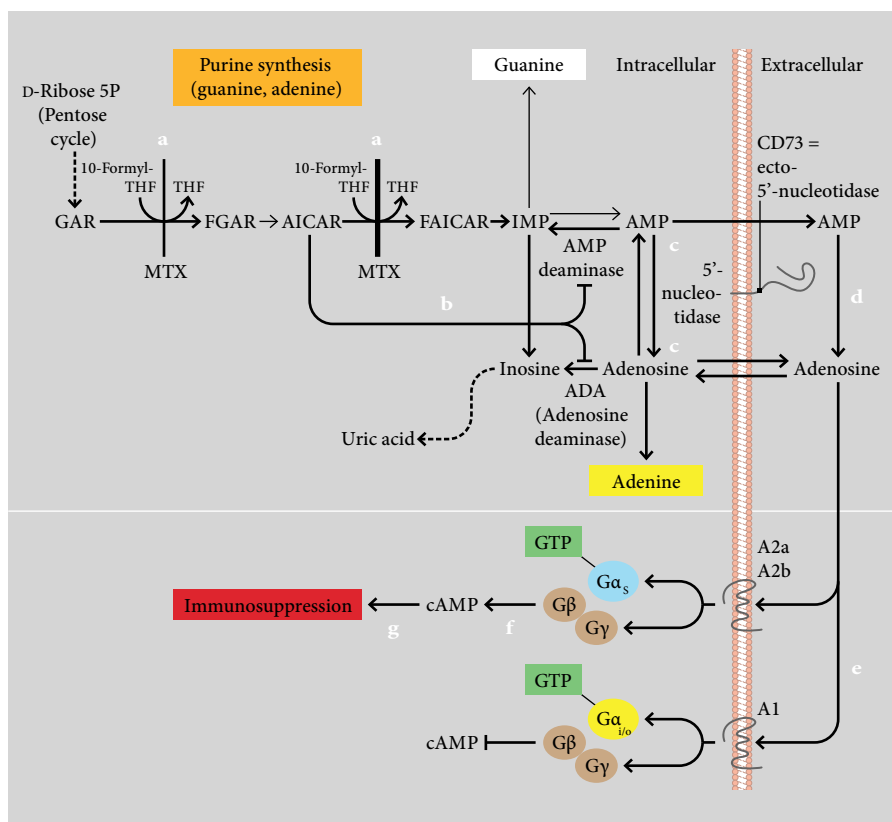


Figure 9.4 Main mechanisms of action of methotrexate. (a) Strong inhibition of AICAR→FAICAR results in the accumulation of AICAR. (b) Accumulated AICAR inhibits AMP deaminase and adenosine deaminase (ADA). (c) Adenosine is increased in the intracellular space. (d) Intracellular accumulation of adenosine eventually leads to increased concentration of adenosine in the extracellular space. (e) Adenosine binds to receptors A1, A2a, and A2b. (f) Cyclic adenosine monophosphate (cAMP) accumulates in the cell. (g) Higher concentrations of cAMP lead to immunosuppression. AICAR, 5-amino-1- β -D-ribofuranosyl-imidazole-4-carboxamide; AMP, adenosine monophosphate; CD73, cluster of differentiation 73; FAICAR, 5-formamidoimidazole-4-carboxamide ribotide; FGAR, formyl-glycineamide ribonucleotide; GAR, glycineamide ribonucleotide; IMP, inosine monophosphate; MTX, methotrexate. Reproduced with permission from Cutolo et al [13] ©BMJ.

Area/compartiment	Effect/mechanism
Enzymes	1. Inhibits DHFR 2. Inhibits AICAR 3. Increases the release of adenosine 4. Inhibits COX-2 synthesis (indirectly)
Cytokines	1. Inhibits IL-8 in PBMC 2. Decreases IL-6 levels 3. Decreases IL-1 activity 4. Decreases production of leukotriene B4 5. Increases gene expression of IL-4 and IL-10 6. Decreases gene expression of Th1 cytokines
Synovial tissue	1. Decreases monocytic cell growth 2. Indirect inhibitory effects on synovial MMP 3. Stimulates inhibitors of MMP (TIMP)

Table 9.1 Effects/mechanism of action of methotrexate. AICAR, 5-amino-1- β -D-ribofuranosyl-imidazole-4-carboxamide; COX-2, cyclooxygenase-2; DHFR, dihydrofolate reductase; IL, interleukin; MMP, matrix metalloproteinases; PBMC, peripheral blood mononuclear cells; Th1, T helper type 1; TIMP, tissue inhibitor of metalloproteinases.

Drug group	Interaction	Reference
Sulfa drugs	Severe folate deficiency	[22]
Salicylates	Competitors of binding proteins	[23]
NSAIDs	Effect on renal clearance	[24]
Leflunomide	Liver toxicity	[25]
Azathioprine	Liver toxicity, GI side effects	[26]

Table 9.2 Interactions of methotrexate with other drugs. NSAIDs, nonsteroidal anti-inflammatory drugs; GI, gastrointestinal.

Methotrexate	Strength	Dose
Oral (tablets)	2.5 mg	5–25 mg weekly (2–10 tablets weekly)
Injectable	25 mg/mL	0.2 mL–1 mL weekly

Table 9.3 Methotrexate dosing.

Methotrexate	LFTs <3X	LFTs >3X	GFR <50 mL/min/1.73m ²	GFR <20 mL/min/1.73m ²
Dose	25–50% (5–10 mg)	Do not use	25–50%	Do not use

Table 9.4 Methotrexate administration and chronic kidney and liver disease. LFT, liver function test; GFR, glomerular filtration rate.

Drug	Onset of action	Efficacy rate (%)
Methotrexate	6–8 weeks	70
Leflunomide	2–3 months	50
Hydroxychloroquine	2–6 months	30–50
Sulfasalazine	2–3 months	30

Table 9.5 Efficacy rate of methotrexate and other disease modifying antirheumatic drugs. Efficacy is measured as the average count of number of tender joints, swollen joints, physician global assessment and the values of erythrocyte sedimentation rate and C-reactive protein levels before and after treatment with methotrexate.

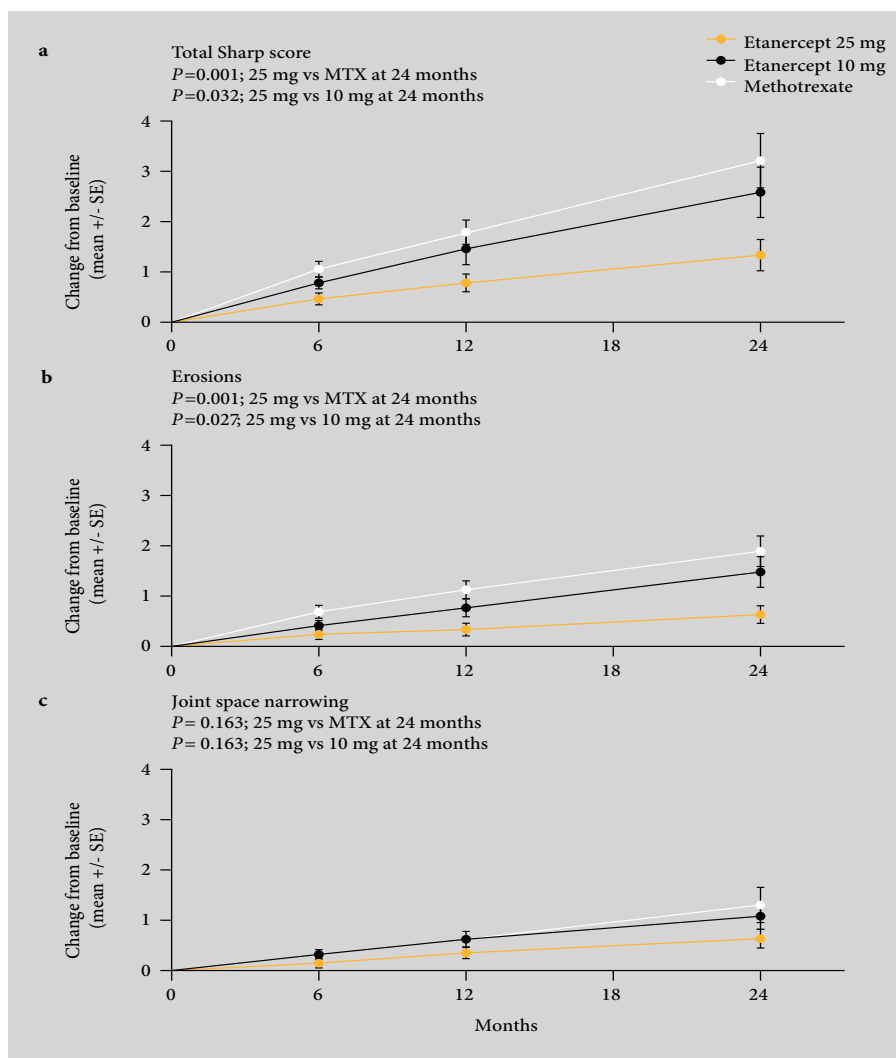


Figure 9.5 Mean changes in (a) Sharp total scores, (b) erosions scores, and (c) joint space narrowing scores in patients treated with methotrexate and etanercept over a 24-month period. MTX, methotrexate. Reproduced with permission from Genovese et al [31] ©Wiley.

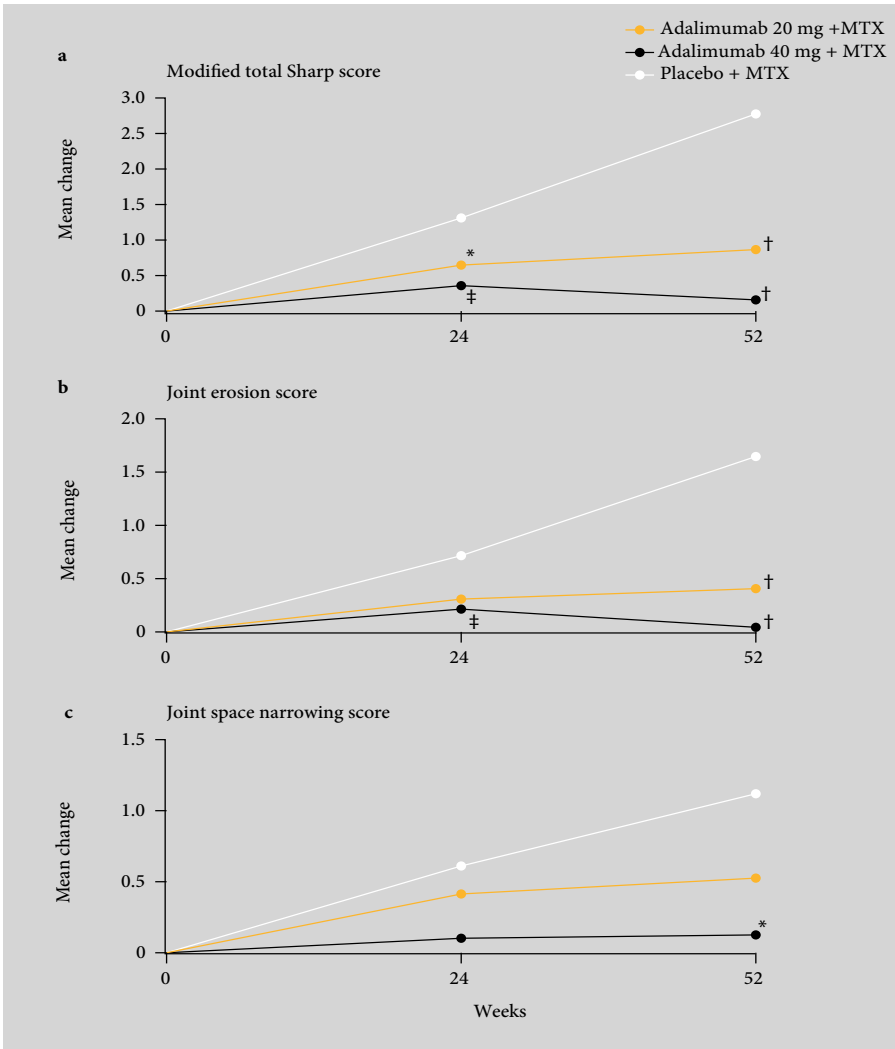


Figure 9.6 Mean changes from baseline to Week 52 in the (a) modified total Sharp radiographic progression score (extrapolated data), (b) erosion scores (last observation carried forward [LOCF] data), and (c) joint space narrowing scores (LOCF data) among the patients receiving adalimumab 40 mg every other week plus methotrexate (MTX), adalimumab 20 mg weekly + MTX, and placebo + MTX. * $P \leq 0.01$; † $P \leq 0.001$; ‡ $P \leq 0.05$ versus placebo (by analysis of covariance, baseline value are the covariates). Adapted with permission from Keystone et al [32] ©Wiley.

Methotrexate treatment	Recommendations
Baseline	CBC with differential and platelets B12 and folate levels Hepatitis B and C serologies Chest radiograph and pulmonary function tests (if clinically indicated) Baseline liver biopsy only if: history of alcohol abuse, elevated transaminases, or history of chronic hepatitis B or C
Monitor (4–8 weeks)	CBC LFTs, albumin, creatinine Liver biopsy if: 5/9 (or 6/12) transaminase determinations are abnormal (over 1 year) and do not subside with a decrease in the weekly dose of MTX, or discontinuation of NSAIDs Decrease in serum albumin (in patients with well controlled RA)

Table 9.6 Methotrexate monitoring guidelines. CBC, complete blood count; LFT, liver function tests; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; RA, rheumatoid arthritis.

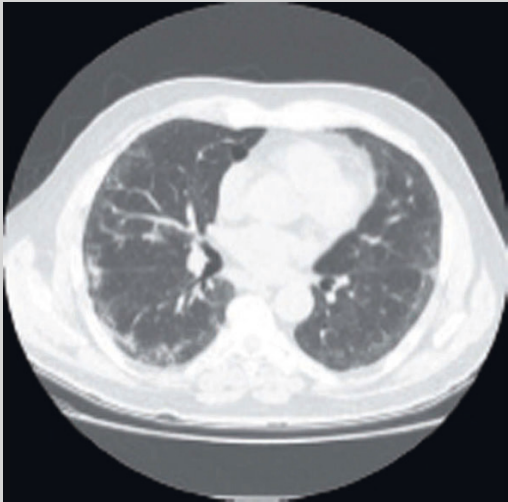


Figure 9.7 Non-specific interstitial pneumonitis pattern after 3 months of therapy with methotrexate.

Organ/system	Side effect
Gastrointestinal tract	Oral ulcers Dyspepsia Abdominal pain Diarrhea Gastrointestinal bleeding
Blood	Macrocytosis Cytopenias
Liver	Elevation of liver function tests Fibrosis Cirrhosis
Lungs	Interstitial pneumonitis Diffuse interstitial fibrosis
Cardiovascular system	Atherogenesis (unclear if methotrexate is the cause)
Central nervous system	Headaches Dizziness Neurocognitive impairment Encephalopathy (rare)
Musculoskeletal system	Myalgias Arthralgias Flu-like symptoms
Skin	Rash Alopecia Actinic keratosis
Genitourinary tract	Erectile dysfunction Gynecomastia
Reproductive system	Abortions Fetal death Aminopterin syndrome
Cancer	Leukemia Lymphoma Lungs
Others	Nodulosis Delayed wound healing Opportunistic infections

Table 9.7 Methotrexate side effects. Reproduced with permission from Alacón et al [33] ©LWW.



Figure 9.8 Oral ulcers in patient treated with methotrexate.

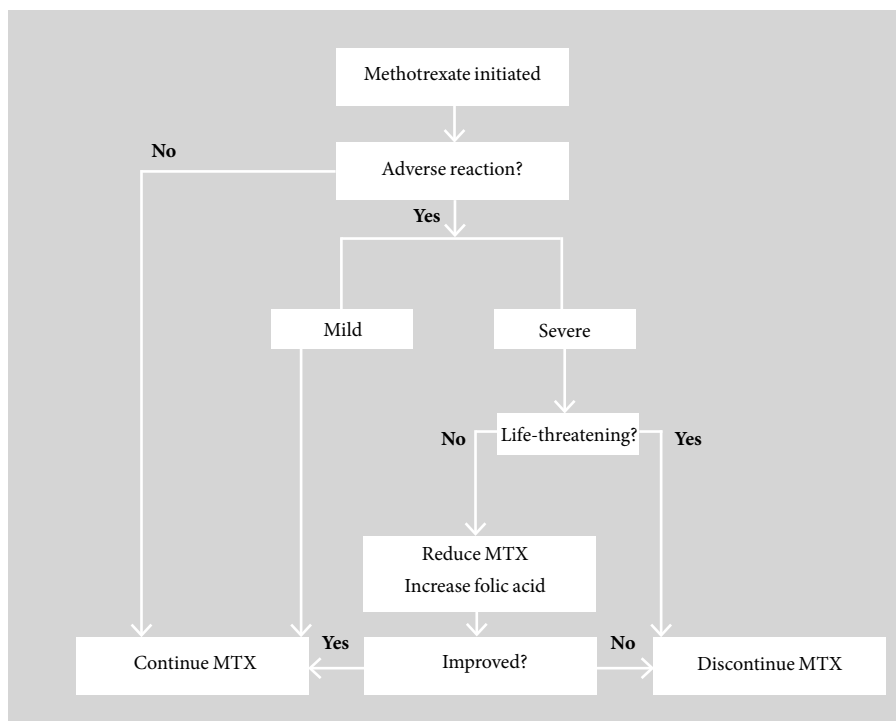


Figure 9.9 Accepted general algorithm for initial approach to management of suspected adverse events related to treatment with methotrexate for rheumatoid arthritis.

Adverse event	Recommendation
Oral ulcers	Increase folic acid dose, dose reduction[41]
Dyspepsia, abdominal pain, diarrhea	Reduce dose, treat symptoms, consider switching to parenteral methotrexate [41]
Gastrointestinal bleeding	Stop methotrexate. Could rechallenge (on a lesser dose) once GI bleeding has been properly treated. Consider proton pump inhibitors. Consider switching to parenteral methotrexate [41]
Macrocytosis	Increase folic acid dose. B12 supplementation if indicated [42]
Cytopenias	For values below 50% of baseline, withhold methotrexate and check CBC weekly. May rechallenge once problem is resolved. Consider higher doses of folic acid and methotrexate dose reduction [43,44]
Elevation of liver function tests	For values less than 3x normal/baseline: reduce the dose and monitor liver function tests more frequently [41,44]. For values higher than 3x normal/baseline: discontinue [41]
Cirrhosis, fibrosis	Methotrexate is contraindicated
Cough, shortness of breath	Discontinue methotrexate [41]
Headaches, dizziness	Reduce methotrexate dose and treat symptoms. Observe. If no resolution, consider discontinuing methotrexate [45]
Arthralgias, myalgias	Symptomatic treatment. May need to reduce dose. Consider higher folic acid dose
Alopecia	If intolerable, discontinue methotrexate [41]
Nodulosis	Discontinue methotrexate. May try D-penicillamine [46]
Neoplasia	Careful monitoring [47]

Table 9.8 Recommendations for the management of methotrexate-related side effects.

Procedure	Action
Dental procedures	
1. Cleaning	1. No need to change dose or day of methotrexate administration
2. Minor oral surgeries	2. Hold methotrexate one week before and one week after procedure [49]
Intra-abdominal surgeries	Hold methotrexate one week before and one week after [50,51]
Elective orthopedic procedures	No need to hold or change day of methotrexate administration [41,47]
Ocular procedures	No need to hold methotrexate [52]
Cardiac procedures	No need to hold methotrexate [53]
'Dirty' or contaminated procedures	Hold methotrexate until situation resolves
Joint replacements	Most surgeons would prefer to hold methotrexate treatment for 2 weeks before and 2 weeks after a procedure for fear of infection and delayed wound healing. However, there is evidence that suggests that it is safe to continue methotrexate in patients undergoing elective surgery [47]

Table 9.9 Recommendations for the use of methotrexate during dental and surgical procedures.

References

1. Alarcón G, Tracy I, Blackburn WD J. Methotrexate in rheumatoid arthritis. Toxic effects as the major factor in limiting long term treatment. *Arthritis Rheum.* 1989;32:671-676.
2. Gubner R, August S, Ginsberg V. Therapeutic suppression of tissue reactivity. Effect of aminopterin in rheumatoid arthritis and psoriasis. *Am J Med Sci.* 1951;221:176-182.
3. Black R, O'Brien W, Van Scott E, Auerbach R, Eisen A, Bunim J. Methotrexate therapy in psoriatic arthritis. Double blind study on 21 patients. *JAMA.* 1964;189:743-747.
4. Hoffmeister R. Methotrexate in rheumatoid arthritis. *Arthritis Rheum.* 1972;15(suppl):114.
5. Williams HJ, Wilkens RF, Samuelson CO, et al. Comparison of low dose oral pulse methotrexate and placebo in the treatment of rheumatoid arthritis. A controlled clinical trial. *Arth Rheum.* 1985;28:721-730.
6. Thompson RN, Watts C, Edelman J, Esdaile J, Russell AS. A controlled two-centre trial of parenteral methotrexate therapy for refractory rheumatoid arthritis. *J Rheumatol.* 1984;11:760-763.
7. Andersen PA, West SG, O'Dell JR, Via CS, Claypool RG, Kotzin BL. Weekly pulse methotrexate in rheumatoid arthritis. Clinical and immunologic effects in a randomized double-blind study. *Ann Intern Med.* 1985;103:489-496.
8. Weinblatt ME, Coblyn JS, Fox DA, et al. Efficacy of low dose methotrexate in rheumatoid arthritis. *N Eng J Med.* 1985;312:818-820.
9. Willkens RF. Resolve: methotrexate is the drug of choice after NSAIDs in rheumatoid arthritis. *Semin Arthritis Rheum.* 1990;20:76-80.
10. Tariq S, Tariq S. Methotrexate in rheumatoid arthritis: can current knowledge and experience justify its use as a first-line disease modifying agent? *Postgrad Med J.* 1993;69:775-780.
11. American College of Physicians. Health and Public Policy Committee. Methotrexate in rheumatoid arthritis. *Ann Int Med.* 1987;107:418-419.
12. Seeger DR, Cosulich DDB, Smith JM, Hultquist ME. Analogues of pteroylglutamic acid. II. 4-amino-derivatives. *J Am Chem Soc.* 1949;71:1297-1301.
13. Cutolo M, Sulli A, Pizzorni C, Serio B. Anti-inflammatory mechanisms of methotrexate in rheumatoid arthritis. *Ann Rheum Dis.* 2001;60:729-735.
14. Baggot J, Morgan S, Ha T, Alarcón G, Koopman W, Krumdieck C. Antifolates in rheumatoid arthritis: a hypothetical mechanism of action. *Clin Exp Rheumatol.* 1993;11:101-109.
15. Cronstein B, Eberle M, Gruber H, Levin R. Methotrexate inhibits neutrophil function by stimulating adenosine release from connective tissue cells. *Proc Natl Acad Sci USA.* 1991;88:2441-2445.
16. Segal R, Mozes E, Yaron M, Tartakovsky V. The effects of Methotrexate on the production and activity of interleukin-1. *Arthritis Rheum.* 1989;32:370-377.
17. Crilly A, McInness AG, Watson J, Capell HA, Madhok R. Interleukin 6 and soluble IL2 receptor levels in patients with rheumatoid arthritis treated with low dose oral methotrexate. *J Rheumatol.* 1995;22:224-226.
18. Sperling RI, Benincaso AI, Anderson RJ, Coblyn JS, Austen KF, Weinblatt ME. Acute and chronic suppression of leukotriene B4 synthesis ex-vivo in neutrophils from patients with rheumatoid arthritis beginning treatment with methotrexate. *Arthritis Rheum.* 1992;35:376-383.
19. Genestier L, Paillot R, Fournel S, Ferraro C, Miossec P, Revillard JP. Immunosuppressive properties of Methotrexate: apoptosis clonal deletion of activated peripheral T cells. *J Clin Invest.* 1998;101:322-328.
20. Markham A, Faulds D. Methotrexate: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in rheumatoid arthritis and other immunoregulatory disorders. *Clin Immunother.* 1994;1:217-244.
21. Felson DT, Chernoff M, Anderson JJ, Weinblatt M, Furst D, Schmid F, et al. The effect of age and renal function on the efficacy and toxicity of Methotrexate in rheumatoid arthritis. *J Rheumatol.* 1995;22:218-223.
22. Maricic M, Davis M, Gall EP. Megaloblastic pancytopenia in a patient receiving concurrent methotrexate and trimetopim-sulfamethoxazole treatment. *Arthritis Rheum.* 1986;29:133-135.
23. Stewart CF, Fleming RA, Germain BF, Seleznick MJ, Evans WE. Aspirin alters methotrexate disposition in rheumatoid arthritis patients. *Arthritis Rheum.* 1991;34:1514-1520.

24. Weinblatt M, Kremer J, Coblyn J, et al. Pharmacokinetics, safety and efficacy of combination treatment with methotrexate and leflunomide in patients with active rheumatoid arthritis. *Arthritis Rheum.* 1999;42:1322–1328.
25. Wilkens R, Urowitz M, Stablein D, et al. Comparison of azathioprine, methotrexate, and the combination of both in the treatment of rheumatoid arthritis. *Arthritis Rheum.* 1992;35:849–856.
26. Ellman M, Hou S, Ginsberg D. Low dose methotrexate and severe neutropenia in patients undergoing renal dialysis. *Arthritis Rheum.* 1990;33:1060–1061.
27. Firestein GS. Rheumatoid Arthritis. In: Nabel EG, ed. *ACP Medicine*. Hamilton, ON: BC Decker; 2010.
28. Kremer JM, Lee JK. A long-term prospective study of the use of methotrexate in rheumatoid arthritis. Update after a mean of fifty-three months. *Arthritis Rheum.* 1992;31:577–584.
29. Weinblatt ME, Trentham DE, Frase PA, et al. Long-term prospective trial of low-dose methotrexate in rheumatoid arthritis. *Arthritis Rheum.* 1988;31:167–175.
30. Kremer JM, Phelps CT. Long-term prospective study of the use of methotrexate in the treatment of rheumatoid arthritis . Update after a mean of ninety months. *Arthritis Rheum.* 1992;35:138–145.
31. Genovese MC, Bathon JM, Fleischmann RM, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. *Arthritis Rheum.* 2002;46:1443–1450.
32. Keystone E, Kavanaugh E, Sharp J, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week-trial. *Arthritis Rheum.* 2004;50:1400–1411.
33. Alarcón GS. Methotrexate: its use for the treatment of rheumatoid arthritis and other rheumatic disorders. In: Koopman WJ, ed. *Arthritis and Allied Conditions*. 13th edn. Pennsylvania: Williams & Wilkins; 1996.
34. Kremer JM, Galivan J, Streckfuss A, Kamen B. Methotrexate metabolism analysis in blood and liver of rheumatoid arthritis patients. Association with hepatic folate deficiency and formation of polyglutamates. *Arthritis Rheum.* 1986;29:832–835.
35. Hassan W. Methotrexate and liver toxicity: role of surveillance liver biopsy. Conflict between guidelines for rheumatologists and dermatologists. *Ann Rheum Dis.* 1996;55:273–275.
36. Rosenberg P, et al. Psoriasis patients with diabetes type 2 are at high risk of developing liver fibrosis during methotrexate treatment. *J Hepatol.* 2007;46:1111–1118.
37. Rustin GJ, Booth M, Dent J, Salt S, Rustin F, Bagshawe KD. Pregnancy after cytotoxic chemotherapy for gestational trophoblastic tumours. *Br Med J.* 1984;288:103–106.
38. Organization of Teratology Information Specialists (OTIS). Methotrexate and Pregnancy. OTIS website. www.otispregnancy.org/methotrexate-and-pregnancy-p150081. Accessed March 6, 2015.
39. Kocharla L TJ, Weiler T, Ting T.V, Luggen M, Brunner HI. Monitoring methotrexate toxicity in juvenile idiopathic arthritis. *J Rheumatol.* 2009;36:2813–2818.
40. Hishberg B, Muszkat M, Schlesinger O, Rubinow A. Safety of low dose methotrexate in elderly patients with rheumatoid arthritis. *Postgrad Med J.* 2000;76:787–789.
41. Albrecht K, Muller-Ladner U. Side effects and management of side effects of methotrexate in rheumatoid arthritis. *Clin Exp Rheumatol.* 2010;28(suppl 61):S95–S101.
42. North Derbyshire Prescribing Strategy Group. Rheumatology shared care guidelines: methotrexate. Information sheet for GPs. www.derbyshiremedicinesmanagement.nhs.uk/clinical_guidelines/shared_care_guidelines. Accessed March 6, 2015.
43. Pavy S, Constantin A, Pham T, et al. Methotrexate therapy for rheumatoid arthritis: clinical practice guidelines based on published evidence and expert opinion. *Joint Bone Spine.* 2006;73:388–395.
44. Weinblatt M, Trentham D, Frase Pea. Long-term perspective trial of low dose methotrexate in rheumatoid arthritis. *Arthritis Rheum.* 1988;31:167–175.
45. Weinstock-Guttman B, Nair D, Cohen J. Neurologic complications of immunosuppressive and anti-inflammatory therapy for rheumatic diseases. *J Clin Rheumatol.* 1996;2:268–278.
46. Dash S, Seibold J, Tiku M. Successful treatment of methotrexate induced nodulosis with D-penicillamine. *J Rheumatol.* 1999;26:1396–1399.

47. Visser K, Katchamart W, Loza E, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systemic literature research and expert opinion of a broad international panel of rheumatologists in 3E Initiative. *Ann Rheum Dis.* 2009;68:1086-1093.
48. Steuer A, Keat A. Perioperative use of methotrexate-a survey of clinical practice in the UK. *Br J Rheumatol.* 1997;36:1009-1011.
49. Buch T. Dental procedure Dos and Dont's for RA patients. Everyday Health Website. www.everydayhealth.com/rheumatoid-arthritis/specialists/dental-procedure-dos-and-donts-for-ra-patients.aspx. Accessed March 6, 2015.
50. Heldman F, Braun J. Perioperative use of methotrexate. *Clin Exp Rheumatol.* 2010;28(5 suppl 61):S110-S113.
51. Kumar A, Auron M, Aneja A, et al. Inflammatory bowel disease: perioperative pharmacological considerations. *Mayo Clin Proc.* 2011;86:748-757.
52. Bingham C, Ruffing V. Rheumatoid arthritis treatment. John Hopkins Medicine website. www.hopkinsarthritis.org/arthritis-info/rheumatoid-arthritis. Accessed March 6, 2015.
53. Pieringer H, Stuby U, Biesenbach G. Patients with rheumatoid arthritis undergoing surgery: how should we deal with antirheumatic treatment? *Semin Arthritis Rheum.* 2006;36:278-286.

10 Immunotherapy

Sarah C Horton, Maya H Buch

Introduction

The mainstay of treatment for rheumatoid arthritis (RA) — use of disease-modifying antirheumatic drugs (DMARDs) — affects a range of cellular targets in the immune system. Conventional synthetic or nonbiological DMARDs (nbDMARDs), so-called for their ability to modulate the impact of the disease on joint damage, have historically been discovered through experimental use. Their mechanisms of action in the immune system, however, have not yet been fully elucidated. Increased understanding of the pathogenesis of RA has led to the development of biological DMARDs (bDMARD), with specific targets including cytokines, immune cells, and immune pathways. Over the last 15 years, the availability of highly effective biologic therapies and evolution of management principles to diagnose and treat early and aggressively, using nbDMARDs and bDMARDs, has led to markedly improved patient outcomes [1]. Such an approach not only results in greater disease control, but reduces long-term corticosteroid use and its associated complications, as well as impacting the systemic manifestations and comorbidities associated with chronic RA [1]; in particular, increased cardiovascular disease has emerged as an area of significant concern that could be moderated by optimal disease control [2,3]. Remission is now accepted as a realistic goal for patients with RA, with recent guidelines recommending escalation of therapy in patients who are not achieving a predefined target (ideally remission) [4].

The efficacy of bDMARDs was initially demonstrated in patients with established RA resistant to conventional DMARDs, including methotrexate

(MTX). Those currently licensed for use in Europe and the United States for this indication include several tumor necrosis factor (TNF)- α inhibitors, tocilizumab (an interleukin [IL]-6 receptor inhibitor), and abatacept (an inhibitor of T cell co-stimulation). Rituximab, a B-cell depleting therapy, is licensed for use in patients who have had an inadequate response or intolerance to a TNF inhibitor.

With advances in clinical research demonstrating the importance of early aggressive treatment of RA to prevent long-term disability, bDMARDs have also been trialled in early RA (initially in MTX-naïve patients with poor prognosis, and more recently, short-term use of TNF inhibitors for the purpose of remission induction). Consequently, a number of TNF inhibitors are now approved for severe progressive RA prior to the failure of nbDMARDs, including MTX. Evidence-based guidelines published by the American College of Rheumatology (ACR) recommend TNF inhibitors as first-line therapy in patients with high disease activity and features of poor prognosis [5].

The most commonly used nbDMARDs are MTX, sulfasalazine, hydroxychloroquine, and leflunomide and their immune mechanisms will be reviewed. This chapter will also discuss advances in the understanding of immunopathogenic mechanisms in RA which have steered the development of several bDMARD therapies. Efficacy of such therapies in major Phase III trials in patients with MTX-inadequate response, as well as MTX-naïve patients with poor prognosis, is also summarized.

Use of immunotherapies that target pathways in the innate and adaptive immune system is associated with potential safety concerns, not least infection and malignancy [6–11]. Although placebo-controlled trial data available for biologic therapies have been largely reassuring [12–19], the short-term follow-up and selection of patients in these studies must be considered. Evidence for the long-term safety of these agents is beginning to emerge from observational cohorts and national registries [7–11, 20], in particular for TNF inhibitors, which have been in use the longest amongst biologic therapies. Safety considerations influencing choice of therapy, such as comorbidities and pregnancy, are also highlighted here.

Nonbiologic disease-modifying antirheumatic drugs

Methotrexate

As discussed in Chapter 9, MTX is a folate antimetabolite. Low-dose MTX for the treatment of RA may also act through suppression of T cell activation and decreased expression of adhesion

molecules by such cells via inhibition of alternative enzymes involved in purine metabolism and the subsequent accumulation of adenosine [21]. MTX is considered the ‘anchor’ drug in the management of RA. Evidence-based guidelines published by the European League Against Rheumatology (EULAR) recommend MTX as first-line therapy, unless contraindications are present [22], while other groups recommend initiating MTX in combination with other nbDMARDs [23]. Results of meta-analyses differ regarding whether or not the combination of MTX with other nbDMARDs is more effective than MTX alone; potentially, inclusion of a corticosteroid in combination strategies may be responsible for the benefit observed with these regimens [24,25]. However, it is accepted that efficacy of particular biologics (including TNF inhibitors) is augmented when combined with MTX when compared to biologic monotherapy alone [26].

Sulfasalazine

Sulfasalazine was initially used in RA due to its antibacterial properties in the context of a hypothesis that there was an infectious etiology for RA. The mechanism of action of sulfasalazine is not fully understood. In vitro, anti-inflammatory and immunomodulatory effects of sulfasalazine have been demonstrated including inhibition of lymphocyte migration, T cell proliferation, and activation of B cells [27]. However, sulfasalazine is poorly absorbed from the gut into the bloodstream; it is broken down by intestinal flora into metabolites 5-aminosalicylic acid, equally poorly absorbed, and sulfapyridine. Possible explanations for the efficacy of oral sulfasalazine include a potential effect at the level of the gut-associated lymphoid tissue or an effect of the absorbed metabolite sulfapyridine, blood levels of which are known to correlate with side effects of the drug [28]. Due to potential safety concerns with MTX, sulfasalazine may be the preferred first-line drug for some patients.

Hydroxychloroquine

Hydroxychloroquine is an antimalarial drug. As a lipophilic weak base, similar to other antimalarial agents, it is thought to permeate plasma membranes and accumulate in intracellular lysosomes, with the resultant alteration in pH inhibiting proteases and affecting phagocytosis. More recently, an alternative mechanism of action has been proposed; evidence has emerged that hydroxychloroquine inhibits the stimulation of toll-like receptors (TLRs), in particular TLR9 (ie, receptors which induce inflammatory responses through activation of the innate immune system) [29]. The onset of action of hydroxychloroquine is delayed in comparison

to other nbDMARDs (2–4 months, compared to 6–8 weeks), and it appears to lack the ability to significantly slow radiographic progression when used alone. Consequently, hydroxychloroquine monotherapy tends to be reserved for a select subset of patients, such as those who are elderly, have multiple comorbidities, and/or those with characteristics of mild disease.

Leflunomide

Leflunomide is a relatively new drug in comparison to other nbDMARDs. Through inhibition of de novo pyrimidine synthesis (inhibiting the mitochondrial enzyme dihydroorotate dehydrogenase), it prevents the proliferation of activated lymphocytes, whilst other replicating cells are capable of recycling ribonucleotides and are, therefore, less dependent on de novo synthesis [30]. Its active metabolite, A771726, has a long plasma half-life (15–18 days). In the instance of the need for rapid drug elimination, clearance is possible using oral cholestyramine (8 g three times daily for 11 days).

Biologic disease-modifying antirheumatic drugs

Pathogenesis of rheumatoid arthritis and targets of action

It is known that abnormalities in the immune system may pre-date the onset of clinical synovitis by several years. These include development of autoantibodies including anti-citrullinated peptide antibodies (ACPA) [31,32] and T cell abnormalities [33]. Although the trigger in the development of synovitis is as yet unknown, once it is established, synovial macrophages and fibroblasts play key roles in the perpetuation of inflammation and destruction of articular cartilage and bone through complex cytokine networks (Figure 10.1) [34]. A summary of bDMARDs licensed for use is presented in Table 10.1.

Tumor necrosis factor inhibitors

TNF- α has been recognized since the 1980s as a pivotal cytokine in synovial inflammation, with TNF inhibitors acting upstream within the cytokine network [35]. TNF- α and IL-6 (inhibited by tocilizumab) are pleiotropic cytokines, with multiple roles in the mediation of inflammation and destruction of cartilage and bone. The major producers of these cytokines in the inflamed joint are neutrophils and macrophages.

The first biologic therapy to become available was the TNF inhibitor etanercept, shortly followed by infliximab. For a proportion of patients, however, TNF inhibitor therapy is not effective, either from the outset (primary nonresponse), or with a loss of efficacy over time (secondary nonresponse) [36]. TNF inhibitors may also be inappropriate for some patients due

to safety concerns. The need for alternative treatment options fuelled the development and subsequent introduction of alternative biologic therapies in RA, including alternative TNF inhibitor therapies with alternative routes and/or frequencies of administration (eg, adalimumab, certolizumab, and golimumab).

Over and above introducing a choice in regimen, differences in the structure of TNF inhibitors infer differences in their modes of action (Figure 10.2) [37], which has implications for their efficacy (poor response to one TNF inhibitor does not denote poor response to others) and safety. For example, etanercept has been associated with a lower risk of tuberculosis reactivation and certolizumab may be less likely to cross the placenta than other TNF inhibitors (perhaps due to its lack of the fixed fragment [Fc] of immunoglobulin) [38,39].

TNF- α acts through binding to two receptors (p55 and p75) that form dimers at the cell surface. In vitro assays suggest that whilst all TNF inhibitors bind soluble and membrane-bound TNF- α , preventing binding and activation of the p55 and p75 receptors, the potency of binding varies amongst the agents: certolizumab pegol and the monoclonal antibodies inhibit the effects of membrane-bound TNF- α in a concentration-dependant manner, whilst etanercept was found to be two-fold less potent [40]. This may be significant, as binding to membrane-bound TNF- α may not only block the actions of TNF- α , but also activate the cell (reverse signaling), potentially inducing apoptosis [41]. Furthermore, the Fc component of the monoclonal antibodies enables two other modes of action that could potentially result in additional immunosuppression; the fixation of complement and therefore lysis of leucocytes that express surface-bound TNF- α , and binding to Fc receptors on leucocytes (affecting processes such as phagocytosis, antibody-dependant cytotoxicity, degranulation and cytokine release) [41,42]. Despite possession of an Fc fragment, fixation of complement by etanercept has not been demonstrated consistently, and binding to Fc receptors occurs to a lesser extent (perhaps because of the conformational or steric differences of the Fc component in this molecule) [41].

Rituximab

Rituximab selectively depletes CD20-expressing cells (the majority of B cell subtypes, except those in the very early stages of development and plasma cells). Binding rituximab to CD20 causes destruction of B cells through complement-mediated cytotoxicity (with induction of the membrane attack complex), as well as antibody-dependant cell-mediated cytotoxicity (eg, phagocytosis and direct cell lysis) (Figure 10.3) [43]. Rituximab causes almost complete depletion of B cells in the blood, which, although transient, lasts for several months [44], as

well as partial depletion in the bone marrow and synovial tissue. This drug is discussed in more detail in Chapter 11.

Abatacept

Abatacept inhibits the activation of naïve T cells (Figure 10.4) [45]. For T cell activation, a co-stimulatory signal is necessary in addition to T cell receptor binding to the antigen complex with MHC. This is produced by binding of a CD28 molecule on the T cell surface to CD80/CD86 molecules on the surface of an antigen-presenting cell. T cells are capable of expressing cytotoxic T-lymphocyte antigen 4 (CTLA 4), which binds to CD80/CD86 more readily than CD28, thereby preventing this second process. Abatacept, containing the extracellular domain of CTLA 4, therefore inhibits activation of naïve T cells, but may also prevent the T cell from inducing maturation of autoreactive B cells [46].

Tocilizumab

The binding of tocilizumab to IL-6 receptors (soluble and membrane-bound) prevents the binding of IL-6, therefore preventing formation of dimers of gp130 (a transmembrane glycoprotein) and the subsequent activation of intracellular mechanisms of signal transduction (Figure 10.5) [47]. Amongst its many roles, IL-6 is involved in differentiation of B cells into plasma cells and activation of T cells [48,49].

Efficacy in established rheumatoid arthritis

The primary outcome measure used in pivotal Phase III trials, 20% improvement in the ACR response criteria (ACR20), was met in approximately 60% of patients receiving TNF inhibitors in combination with MTX [12–16]. ACR20, although reliable at discriminating active treatments from placebo effects and commonly used as the primary outcome measure in randomized controlled trials (RCTs) of RA treatment, is of limited use for measuring the status of disease activity in an individual patient. By contrast, the Disease Activity Score (DAS), a composite measure including tender and swollen joint counts, patient global assessment, and a biochemical inflammatory marker, relates to the prevailing disease state and is useful in clinical practice. A Disease Activity Score in 28 joints (DAS28) of less than 2.6 and other measures of clinical remission are reported in more recent trials [16].

A significant difference in ACR20 response and/or components of the ACR was observed with TNF inhibitors (in comparison to placebo/MTX groups), from as early as the first

assessment (week 1 observed in ARMADA [15], RAPID 1 [13], and Weinblatt et al [12]; week 2 in ATTRACT [14]; and week 4 in GO-FORWARD [16]). The aforementioned studies are summarized in Figure 10.6 [12–16].

In addition to clinical efficacy, radiographic outcomes were also assessed in several of these trials, demonstrating superior efficacy of TNF inhibitors in retardation of radiographic progression of joint damage [13,14], with the exception of golimumab in GO-FORWARD [16]. This may be explained by the low rate of progression in the placebo/MTX group, potentially due to the favorable baseline characteristics of patients (including low baseline C-reactive protein, associated with decreased risk of radiographic progression), and the study design, which included X-ray assessment as early as week 16 in non-responders [16]. Radiographic data in trials of TNF inhibitors suggest these drugs confer protection against damage even amongst non-responders [50].

Similar to TNF inhibitors, ACR20 response rates with other bDMARDs (rituximab, abatacept, and tocilizumab) range between 50–70% (Figure 10.7) [17–19]. The DANCER trial investigated rituximab with MTX, with or without glucocorticoids [17]. After 4 weeks, clinical response was not significantly affected by glucocorticoid treatment, but steroids did ameliorate acute infusion reactions. Results are shown for rheumatoid factor-positive patients only, as an analysis of rheumatoid factor-negative patients (85 out of 465 patients) revealed no superior efficacy over placebo (48% achieved ACR20 at 24 weeks compared to 52% of controls), hence their results were excluded from the main analysis [17].

The AIM study also assessed radiographic change, showing approximately 50% reduction in the progression of radiographic damage when abatacept was added to MTX treatment; the median change in total Genant-modified Sharp score from baseline was 0.25 with abatacept plus MTX, compared to 0.53 with MTX therapy alone ($P=0.012$) [18].

Tocilizumab was assessed both alone and in combination with MTX in the CHARISMA trial; the greatest improvement was seen in those treated with tocilizumab plus MTX (ACR20 achieved in 74%, compared to 63% with tocilizumab alone and 41% with placebo plus MTX; $P=0.001$ for tocilizumab plus MTX; $P<0.05$ for tocilizumab alone versus placebo plus MTX) [19]. A subsequent RCT, ACT-RAY, has shown comparable efficacy between tocilizumab in combination with MTX and tocilizumab monotherapy, with no statistically significant difference observed in the primary endpoint, DAS28 remission at 24 weeks (40% versus 35%, respectively; $P=0.19$) [51].

Meta-analyses confirm the efficacy of bDMARDs used in combination with MTX in comparison to MTX monotherapy [26]. In a systematic literature review, 16 trials were identified and 6-month ACR responses were pooled (Figure 10.8); the overall relative risks (95% confidence intervals [CI]) for ACR20, ACR50, and ACR70 were 2.16 (1.83–2.55), 3.20 (2.6–3.95), and 4.82 (2.43–9.57). Radiographic progression at 12 months was lower for patients receiving combination therapy with MTX plus infliximab, adalimumab, certolizumab pegol, abatacept, and tocilizumab versus MTX monotherapy.

Efficacy of bDMARDs has been demonstrated in patients failing previous TNF inhibitor therapy (Figure 10.9) [52–55]. Rates of clinical response are impressive considering these patients may have failed multiple TNF inhibitors in the past; the proportion of patients receiving two or more TNF inhibitors previously was 34% in GO-AFTER [52], 40% in REFLEX [53], and 50% in RADIATE [54].

Golimumab is unique amongst the TNF inhibitors, with RCT evidence of its efficacy in patients with inadequate response to alternative TNF inhibitors [52]. Over half of patients in the study had received previous TNF inhibitor treatment, which was stopped due to lack of efficacy, and approximately one-third of patients had received more than one TNF inhibitor in the past. A significant difference in the proportion of patients achieving the primary endpoint – ACR20 response at 14 weeks – was demonstrated (35% compared to 18%; $P < 0.001$). This rate of clinical response appears lower in comparison to other agents, although only two-thirds of patients were taking concomitant MTX, and the primary endpoint was earlier in comparison to other studies. Observational data also suggest lower responses to a second TNF inhibitor. The type of nonresponse to the initial TNF inhibitor (primary or secondary lack of efficacy or toxicity) may also be relevant in influencing likelihood of response to a subsequent TNF inhibitor.

Until recently there has been a lack of studies directly comparing efficacy of bDMARDs; however, data are now beginning to emerge. The ADACTA trial assessed efficacy of tocilizumab monotherapy in comparison to adalimumab monotherapy in patients for whom it was inappropriate to continue MTX (for example due to MTX intolerance). The primary endpoint was mean change in DAS28 from baseline at 24 weeks; mean change in DAS28 was significantly superior with tocilizumab by an estimate of -1.5 (95% CI; -1.8 to -1.1), by analysis of variance adjusting for confounders including baseline DAS28 and duration of RA (Figure 10.10) [56]. The AMPLE study compared subcutaneous abatacept and adalimumab,

both in combination with MTX, in the treatment of RA in bDMARD-naïve patients with an inadequate response to MTX (Figure 10.11) [57]. The primary endpoint was non-inferiority by ACR20 response at 12 months. The estimated difference between groups was 1.8 (95% CI; 5.6–9.2) supporting non-inferiority.

Efficacy in early rheumatoid arthritis

Inclusion criteria for earlier studies, ASPIRE [58] and PREMIER [59], comprised high disease activity with at least 8–10 swollen joints. Later studies (eg, COMET [60] and GO-BEFORE [61]) included patients with lower levels of activity; moderate disease activity in COMET, and at least four swollen joints (median DAS28 was 2.95–3.31 across groups) in GO-BEFORE. Patient characteristics differed across trials, but generally included presence of at least one poor prognostic factor such as autoantibody positivity (rheumatoid factor or ACPA), radiographic erosion, or raised serum inflammatory markers.

In contrast to response in established disease (Figure 10.7), responses to biologic therapy (+/- MTX) in comparison to MTX monotherapy in early RA appear to be less striking (Figure 10.12) [58–61]. However, this could be predicted due to superior response to MTX in a group that has not been selected for MTX nonresponse. Interestingly, a subanalysis of the COMET study suggests that patients earlier in the disease course may be more responsive to TNF inhibitors in comparison to those with late disease. For example, in the etanercept group, those with ‘very early RA’ (disease duration <4 months) were more likely to achieve remission than those with ‘early RA’ (disease duration of between 4 months and 2 years); frequency of remission was 70% in comparison to 48%, respectively ($P=0.0035$) [62].

Moreover, radiographic data demonstrate additional benefit over and above improvement in clinical symptoms; even with a good clinical response to MTX (ie, 70% improvement in the ACR response criteria [ACR70]), radiographic non-progression was observed in only 43% of cases, in comparison to 72% of ACR70 responders treated with adalimumab and MTX [63]. Similar findings have been observed with other TNF inhibitors, for example with etanercept in the TEMPO trial [64].

The IMAGE study evaluated rituximab (2×500 mg or 2×1000 mg) with retreatment according to disease activity in MTX-naïve patients (disease duration up to 4 years, with presence of at least one poor prognostic factor) [65]. The target of treatment was remission and patients were retreated at or after 24 weeks if they were not in remission (remission: DAS28<2.6).

Remission at 1 year was achieved in 31% of patients receiving rituximab vs. 13% of patients in the control group ($P<0.001$) [65]. During the first 24 weeks, the higher dose (2×1000 mg) group demonstrated significantly superior joint protection compared with placebo, while the lower dose (2×500 mg) conferred numerical, although not statistical, radiographic benefit [65]. Therefore, the primary endpoint (inhibition of radiographic damage as measured by change in Genant-modified Sharp score at 1 year), was met only with the higher dose. Beyond 24 weeks, however, radiographic progression was minimal and similar in both dose groups.

Abatacept (in combination with MTX) was assessed in MTX-naïve patients with early RA (disease duration up to 2 years) and poor prognostic factors (eg, seropositivity for rheumatoid factor and/or ACPA, and presence of radiographic erosions) [66]. Primary endpoints for the study were remission ($\text{DAS28}<2.6$) and Genant-modified total Sharp score at 1 year. DAS28 remission was achieved in 42% of patients in the abatacept and MTX group, compared to 23% taking MTX alone ($P<0.001$) [66]. There was also a significant slowing of radiographic progression (mean change in total score 0.63 vs. 1.06; $P=0.040$).

In the AMBITION study, patients with disease duration >3 months who had previously discontinued MTX or TNF inhibitors for reasons other than inefficacy or a clinically important adverse event could be included [67]. A significantly higher proportion of patients receiving tocilizumab monotherapy achieved the primary endpoint of ACR20 response at 24 weeks (70% compared to 53%; $P<0.0001$), and one-third of patients achieved DAS28 remission, compared to 12% of patients receiving MTX (Figure 10.13) [67].

Cost-effectiveness of immunotherapy in early rheumatoid arthritis

There are a number of limitations to consider when drawing conclusions from economic analyses such as that displayed in Figure 10.14 [68]. Due to a lack of direct head-to-head trials, they largely rely on comparisons of agents between different studies; heterogeneity of included studies may lead to limitations in accurately assessing utility scores, for example. In addition, models simplify a complex situation and may not take into account a number of costs (eg, change in work productivity). Difficulties in interpreting results are evident, as incremental cost-effectiveness ratios for TNF inhibitor therapies vary widely between analyses. Presently, it remains controversial to declare that first-line use of biologics may be cost-effective. Studies suggest very early, short-term use may induce remission, which may be sustained despite biologic withdrawal [69–71]. It is perceivable that early short-term use may offset the need for long-term treatment with several sequential biologic therapies in the most resistant patients.

Recommendations for the use of disease-modifying antirheumatic drug therapies

Several studies support initial MTX monotherapy with a step-up treatment to target regimen to achieve remission or at least a low disease activity state [72,73], as recommended by EULAR (Figure 10.15) [4,5,22]. In the TIGHT CONTROL for Rheumatoid Arthritis (TICORA) study, for example, tight control of disease in the intensive treatment arm proved advantageous over routine treatment; intensive management involved monthly assessment and step-up to combination DMARD therapy according to a target of low disease activity, in comparison to three-monthly monitoring without use of a formal measure of disease activity [72]. At 18 months, clinical remission (as defined by EULAR) was achieved in 65% of the intensive therapy group, compared to 16% of the routine treatment group (although the intensive group also received greater steroid doses). TICORA and other pragmatic studies demonstrate that remission is a realistic goal but it is not always achievable with conventional DMARD therapy alone [73]. In these patients, biologic therapy may be indicated; TNF-inhibitor therapies, and more recently, abatacept and tocilizumab, have been licensed for use in these patients.

The Swedish Pharmacotherapy (SWEFOT) study compared addition of a TNF inhibitor (infliximab) to addition of conventional DMARDs (eg, sulfasalazine and hydroxychloroquine) in patients failing to achieve low disease activity after 3 months of initial MTX monotherapy [74]. The primary endpoint, a good response as defined by EULAR at 1 year, was achieved in significantly more patients randomized to receive infliximab than in those receiving conventional DMARDs (39% compared to 25%; $P=0.016$).

Nevertheless, it remains to be determined whether this approach is optimal to achieve remission. Considering structural outcomes, strategy trials indicate greater inhibition of radiographic damage may be achieved with first-line use of TNF inhibitors [75,76]. Therefore, individuals with poor prognostic factors may derive greater benefit from earlier first-line bDMARD intervention. Which strategy is most appropriate, and in which patients, remains to be determined. There is also increasing attention towards evaluating a bDMARD-induced remission induction approach followed by maintenance with nbDMARD.

The ACR recommends combination therapy (either combination nbDMARDs or a TNF inhibitor combined with MTX) as initial therapy for a subset of patients with poor prognosis (Figure 10.16) [5,22]. The COMBination therapy in Rheumatoid Arthritis (COBRA) study was the first to show a benefit with initial combination DMARD therapy over nbDMARD

monotherapy (in this study, sulfasalazine monotherapy) [77], shortly followed by the Finnish Rheumatoid Arthritis Combination Therapy Trial (FIN-RACo) [78]. The BeSt study, a randomized, single-blind trial compared four treatment strategies in early RA: sequential DMARD monotherapy; initial MTX with step-up to combination DMARD therapy; initial combination nbDMARD therapy with high dose corticosteroid; and initial infliximab with MTX [75]. More rapid clinical improvement was achieved when combination of nbDMARDs or infliximab with MTX was used as a first-line therapy, with less progression of joint damage appearing on radiographs [75]. In cases where disease remained effectively suppressed, drug therapies (preferentially corticosteroids and infliximab in the first instance) were tapered and withdrawn. This was most successful in the group initially treated with infliximab combination therapy: 53% of patients were on a single drug for disease control at the end of the 2-year study (compared to 31–36% in other groups) [75]. The randomized double-blind TEAR trial suggested immediate triple therapy (MTX, sulfasalazine, and hydroxychloroquine) is at least as effective as initial etanercept in combination with MTX in MTX-naïve patients, with no significant differences observed in the primary outcome (DAS28-erythrocyte sedimentation rate [DAS28-ESR] from weeks 48 to 102), between these groups. However, there was an indication that initial etanercept and MTX may be favorable in preventing radiographic progression in comparison to initial triple therapy (no progression observed in 79% vs. 65%) [76].

Safety of immunotherapy

There is an increased risk of infection with the more potent nbDMARDs (eg, MTX and leflunomide) and viral hepatitis B and C screening is recommended in high-risk patients [79]. There is also the potential for these agents to promote myeloid/lymphatic malignancies or solid cancers. Post-marketing reports of lymphoma have been noted [80], but increased risk of lymphoma is inherent with rheumatoid disease itself and other chronic inflammatory conditions.

Regular blood monitoring (eg, full blood count, liver, and renal function tests, every 8–12 weeks) is essential for patients receiving MTX, sulfasalazine, and leflunomide. Leflunomide, particularly when used in combination with MTX, may cause severe liver complications. In 2001, the European Medicines Evaluation Agency reported 296 cases of hepatotoxicity in patients receiving leflunomide (129 considered serious, 2 cases of cirrhosis, 15 cases of liver failure, and 9 fatalities) [81]. Of the serious cases, 78% were concomitantly treated with other hepatotoxic drugs and 33% had other risk factors (including a history of alcohol excess and abnormal liver function) [81].

Yearly ophthalmology assessment is recommended with hydroxychloroquine use. The risk of macular retinopathy is negligible with doses of ≤ 400 mg, but it increases with chronic use (≥ 5 years) and cumulative dose >1000 g [82].

The potential increased risk of malignancy with bDMARDs exists in the context of the established risk associated with RA and other chronic inflammatory diseases. A meta-analysis of 21 observational studies revealed malignancy rates may be increased in patients with RA by an estimate of 5%, compared to the general population when considering all cancers (standardized incidence ratio [SIR] 1.05; 95% CI; 1.01–1.09). Additionally, it is significantly higher for the risk of lymphoma (SIR 2.1; 95% CI; 1.8–2.4), and in particular, Hodgkin's lymphoma (SIR 3.3; 95% CI; 2.6–4.2) [83]. Although data from registries in regard to TNF inhibitors are reassuring [20], channelling bias may be present, with TNF inhibitors being avoided in patients at greatest risk, indicating caution should be exercised in such patients. This issue has begun to be addressed by two studies in which the incidence-rate ratio for recurrence with TNF inhibitors, in comparison to nbDMARDs, was calculated as 0.5 (95% CI; 0.1–2.2) and 1.4 (0.5–5.5) [84,85]. Safety considerations are listed in Tables 10.2 and 10.3 [86–98].

Prospective new targets for immunotherapy

Novel targets for immunotherapies are continuously being identified and evaluated (Table 10.4). Research into the role of several key cytokines in the pathogenesis of RA has led to Phase I and II studies yielding initial data supporting the safety and efficacy of biologics inhibiting their action. These include inhibitors of B cell activating factor [99], IL-17 [100,101], IL-20 [102], and granulocyte-macrophage colony stimulating factor [103]. Insight into the role of regulatory T cells in the suppression of the immune response against self-antigens has also steered biologic drug development, with initial Phase II data for a humanized agonistic monoclonal antibody, BT-061, demonstrating meaningful clinical responses with this drug [104].

In addition to new biologic therapies, small synthetic molecules targeting intracellular proteins involved in autoimmune pathways and phosphodiesterases involved in inflammatory networks are also being investigated. One clear advantage they provide over monoclonal antibodies is the potential option of oral administration. Recently published results of a Phase III trial of tofacitinib demonstrate its efficacy in combination with methotrexate as comparable to adalimumab in patients with active RA despite methotrexate; ACR20 response rate at 6 months was 52% and 53% for tofacitinib 5 mg and 10 mg dose groups, respectively; 47% in those receiving adalimumab; and 28% in placebo controls [105]. Adverse events occurred more

frequently with tofacitinib than with placebo. In November 2012, tofacitinib was approved for use in the US for the treatment of patients with moderate-to-severely active RA who have had an inadequate response to, or who are intolerant of, methotrexate.

In Phase II studies, significant clinical improvements with fostamatinib [106] and masitinib [107] have been reported in patients with an inadequate response to methotrexate or nbDMARDs, respectively. However, in a Phase II trial of fostamatinib in patients previously receiving bDMARD, ACR responses were no different in patients receiving fostamatinib from those receiving placebo at 3 months [108]. After initial proof of concept studies demonstrating potential efficacy of phosphodiesterase-4 inhibitors, Phase I and Phase II studies are currently underway [109]. Further discussion of emerging therapies can be found in Chapter 12.

Mechanism of action	Name	Structure	Year of approval by the EMA
TNF- α inhibition	Etanercept	Fusion protein; extracellular domains of two 75 kDA TNF- α receptors and constant fragment of human immunoglobulin	2000
	Infliximab	Mouse-human chimeric monoclonal antibody against TNF- α	1999
	Adalimumab	Humanized monoclonal antibody against TNF- α	2003
	Certolizumab	Pegylated antibody-binding fragment of immunoglobulin against TNF- α	2009
	Golimumab	Fully human monoclonal antibody against TNF- α	2009
B-cell depletion	Rituximab	Mouse-human chimeric monoclonal antibody against CD20	2006
Inhibition of T cell co-stimulation	Abatacept	Fusion protein; extracellular domain of CTLA-4 and human immunoglobulin	2007
	Abatacept		2012*
Inhibition of IL-6	Tocilizumab	Monoclonal antibody against IL-6 receptor	2009
	Tocilizumab		2014

Table 10.1 Structure and method of administration of biological disease-modifying antirheumatic drugs licensed for use. *Date of approval by European Commission. CD20, cluster of differentiation cell-surface protein 20; CTLA-4, cytotoxic T-lymphocyte antigen 4; EMA, European Medicines Agency; FDA, Food and Drug Administration; IL, interleukin; IV, intravenous; SC, subcutaneous; TNF- α , tumor necrosis factor alpha.

Year of approval by the FDA	Route	Dose and frequency
1998	SC	50 mg weekly or 25 mg twice weekly
1999	IV	3 or 5 mg/kg at 0, 2, and 6 weeks then every 2 months. Weekly methotrexate must be administered to decrease immunogenicity.
2002	SC	40 mg every 2 weeks
2008	SC	400 mg at 0, 2, and 4 weeks then every 4 weeks or 200 mg every 2 weeks
2009	SC	50 mg every 4 weeks
2006	IV	1000 mg at 0 and 2 weeks. Retreatment regimens include retreatment on demand (at time of flare), retreatment to target (according to level of disease activity), or fixed retreatment every 6 months.
2005	IV	10 mg/kg (one of three doses) every 4 weeks
2011	SC	125 mg weekly
2010	IV	4 mg/kg every 4 weeks
2013	SC	162 mg every other week or weekly, according to body weight and response

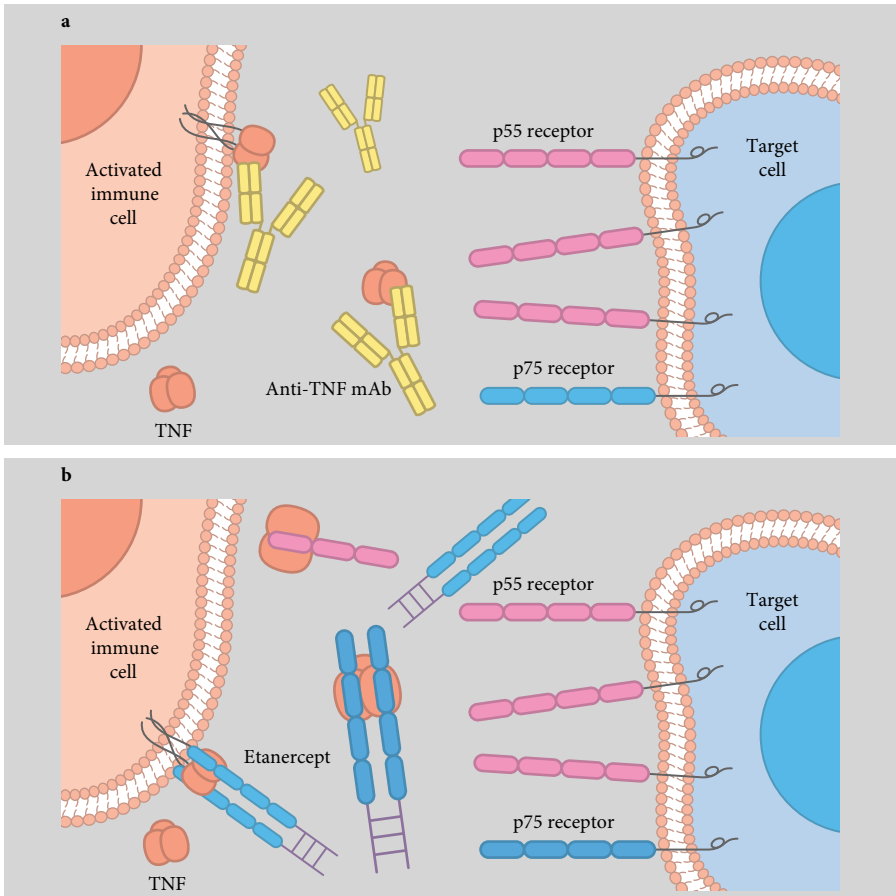


Figure 10.2 Mechanism of action of tumor necrosis factor inhibitors. (a) Monoclonal antibodies (infliximab, adalimumab, golimumab); (b) Fusion protein (etanercept). p55 and p75 receptors: TNF- α receptors; mAb, monoclonal antibody; TNF, tumor necrosis factor. Reproduced with permission from Mease [37] ©Springer.

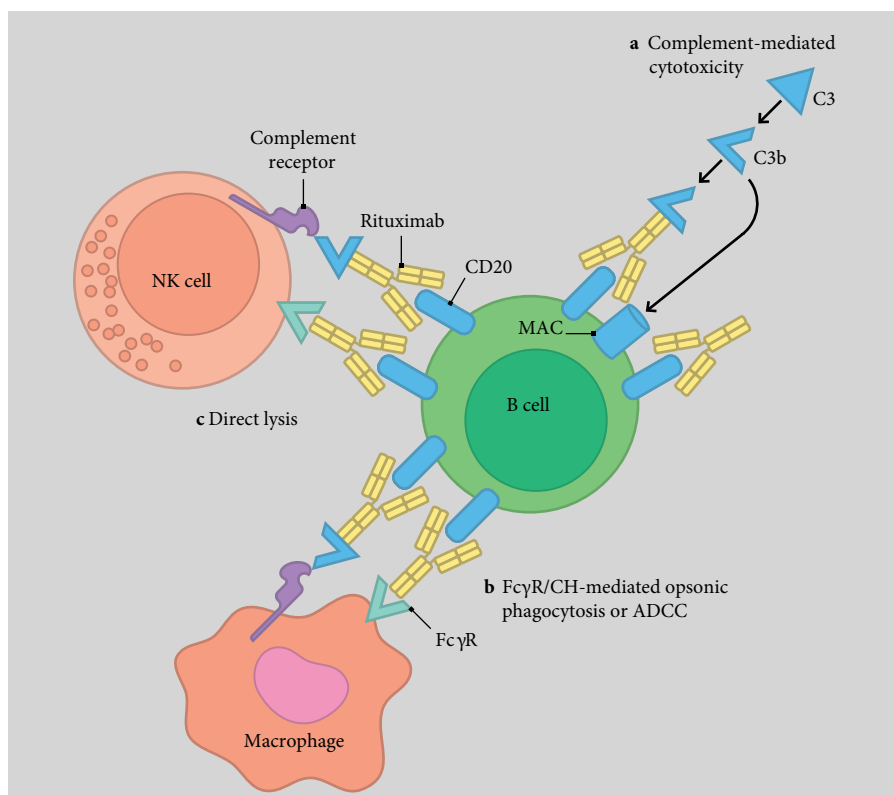


Figure 10.3 Mechanism of action of rituximab. B-cell destruction by rituximab through activation of (a) complement; (b) macrophages; (c) NK cells. ADCC, antibody-dependant cell-mediated cytotoxicity; FcγR, Fc gamma receptor; MAC, membrane attack complex; NK, natural killer cell. Reproduced with permission from Taylor and Lindorfer [43]©Nature.

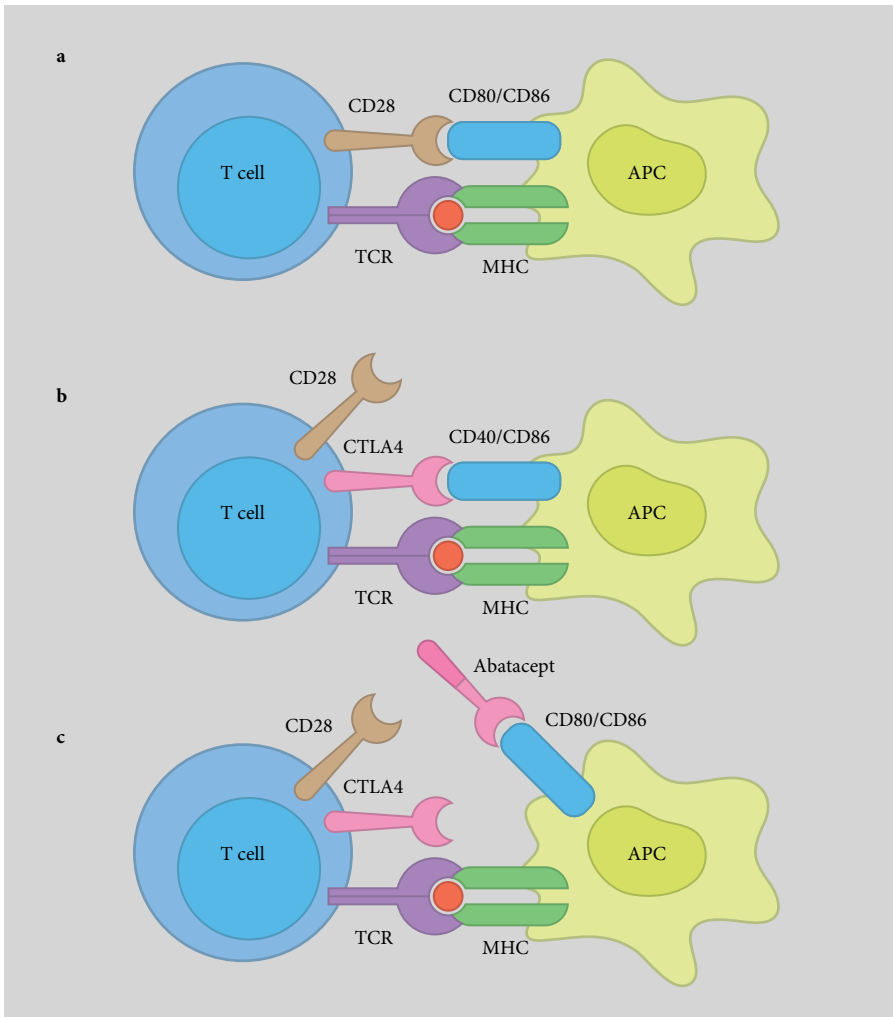


Figure 10.4 Mechanism of action of abatacept. (a) T cell activation through T cell receptor binding to MHC expressed on the surface of an APC, and co-stimulation through CD28 binding to CD80/86; (b) Co-stimulation required for T cell activation prevented by CTLA4; (c) Co-stimulation required for T cell activation prevented by abatacept (CTLA4-immunoglobulin fusion protein). APC, antigen presenting cell; CD, cluster of differentiation; CTLA4, cytotoxic T-lymphocyte antigen 4; MHC, major histocompatibility complex; TCR, T-cell receptor. Reproduced with permission from Ruderman and Pope [45] ©Nature.

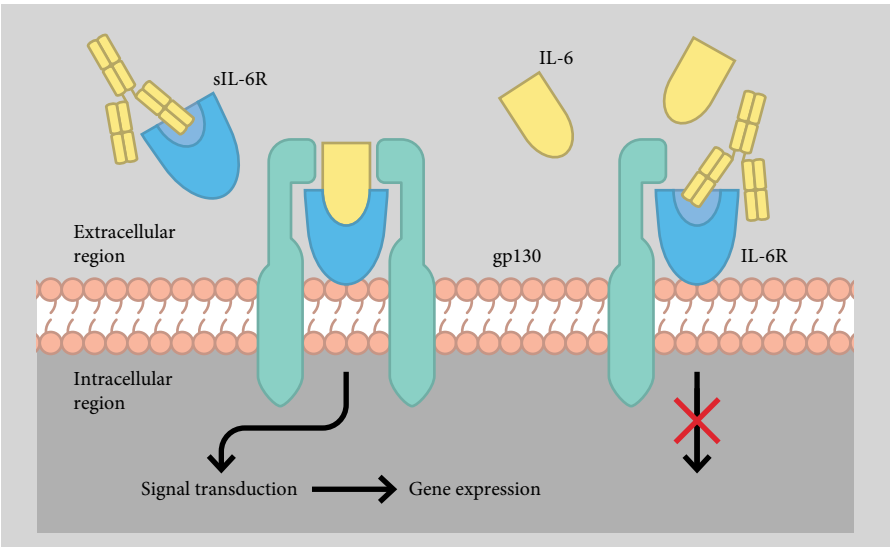


Figure 10.5 Mechanism of action of tocilizumab. Blockade of IL-6 signals by anti-IL-6 receptor antibody tocilizumab. gp130, glycoprotein 130 (transmembrane subunit of cytokine receptor); IL-6R, interleukin-6 receptor (membrane bound); sIL-6R, soluble interleukin-6 receptor. Reproduced with permission from Kishimoto [47] ©BMC.

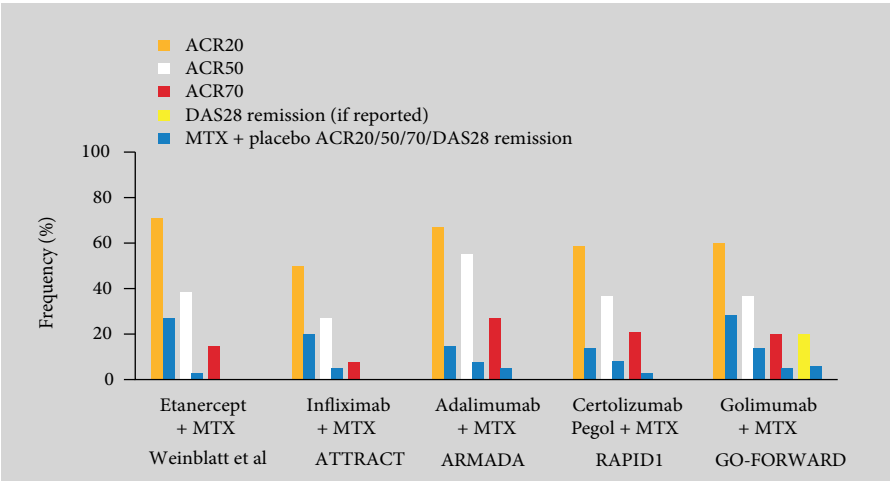


Figure 10.6 Efficacy of tumor necrosis factor inhibitors in combination with methotrexate at 6 months in patients with active rheumatoid arthritis despite methotrexate treatment (methotrexate-inadequate response). Results are shown for licensed dose groups. ACR20/50/70: at least a 20/50/70% improvement in tender joint count, swollen joint count and three of the following: patient pain, patient global disease activity, physician global disease activity, physical function (eg, Health Assessment Questionnaire Disability Index), and acute-phase reactants, erythrocyte sedimentation rate, or C-reactive protein. ACR 20/50/70, American College of Rheumatology 20%; 50%, and 70% improvement criteria; DAS, disease activity score; DAS28, disease activity score based on 28 joints; MTX, methotrexate.

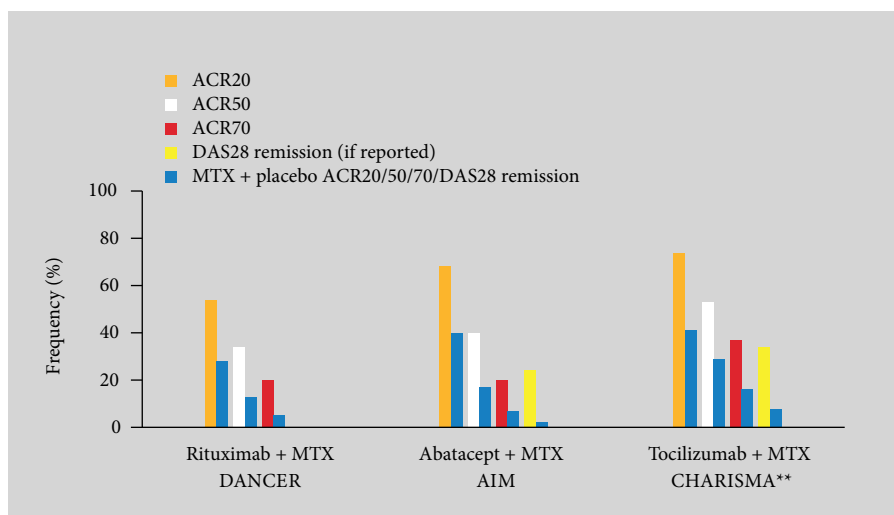


Figure 10.7 Efficacy of non-tumor necrosis factor biological disease-modifying antirheumatic drugs therapies in combination with methotrexate at 6 months in patients with active rheumatoid arthritis despite methotrexate treatment (methotrexate-inadequate response). Results are shown for licensed dose groups. ACR20/50/70: at least a 20/50/70% improvement in tender joint count, swollen joint count and three of the following: patient pain, patient global disease activity, physician global disease activity, physical function (eg, Health Assessment Questionnaire Disability Index), and acute-phase reactants, erythrocyte sedimentation rate, or C-reactive protein. **Study duration in CHARISMA was 16 weeks (outcomes presented for study end). ACR, American College of Rheumatology; DAS28, disease activity score based on 28 joints; MTX, methotrexate.

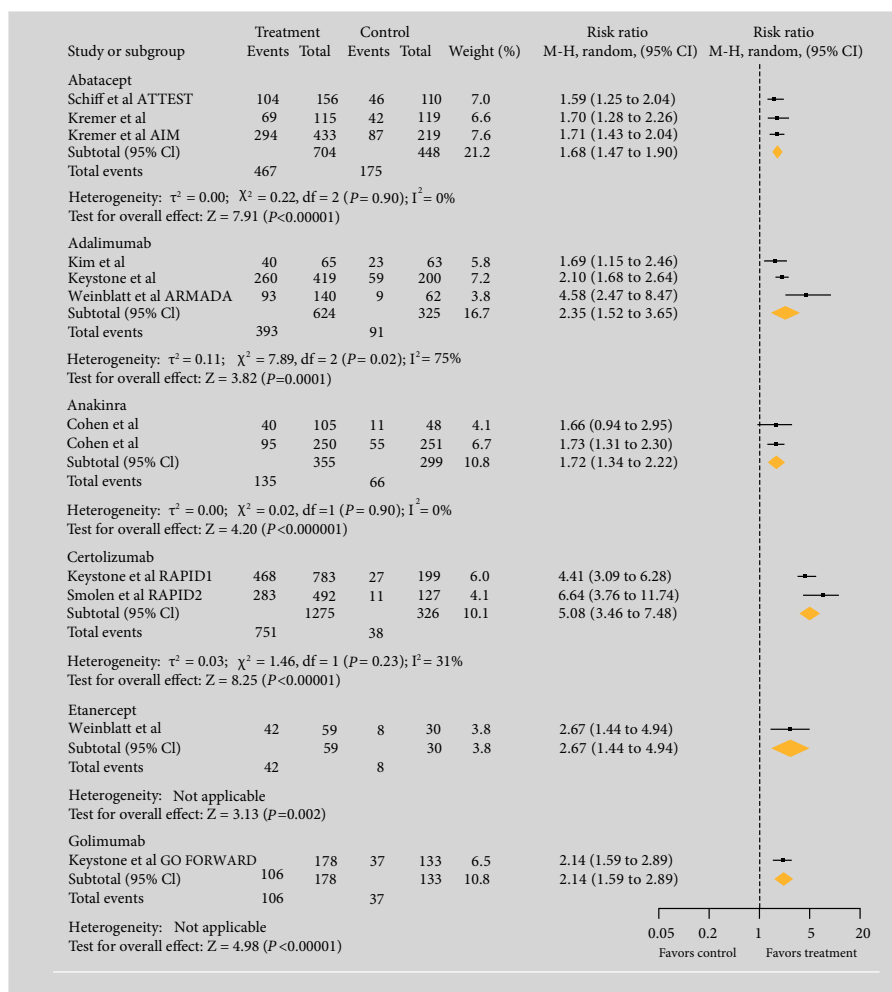


Figure 10.8 Meta-analysis of efficacy of biological disease-modifying antirheumatic drug therapies in combination with methotrexate versus methotrexate monotherapy in patients with active rheumatoid arthritis despite methotrexate treatment (methotrexate-inadequate response): relative risk for ACR20 response at 6 months (*continues overleaf*). ACR20, American College of Rheumatology 20% improvement criteria; CI, confidence interval. Reproduced with permission from Nam et al [26] ©BMJ.

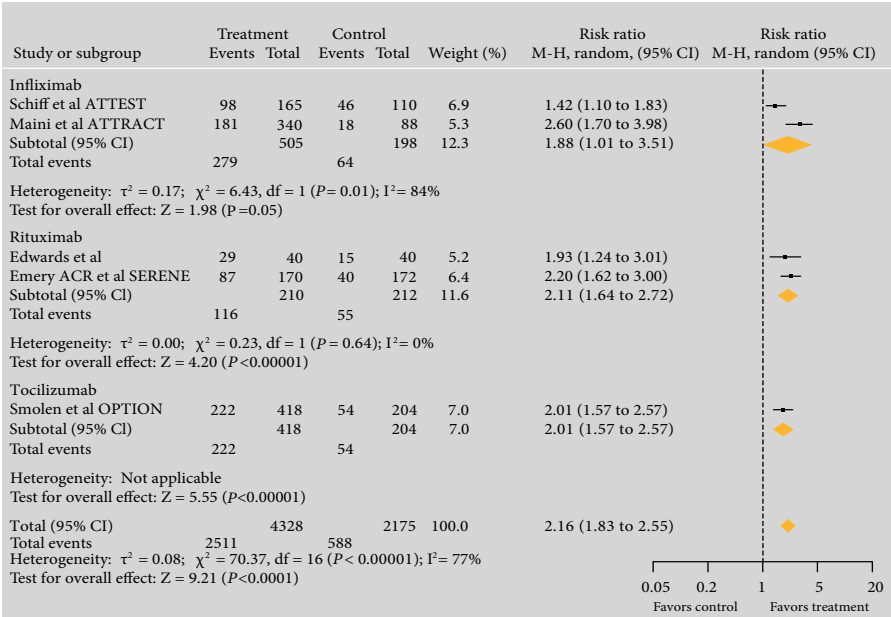


Figure 10.8 (continued).

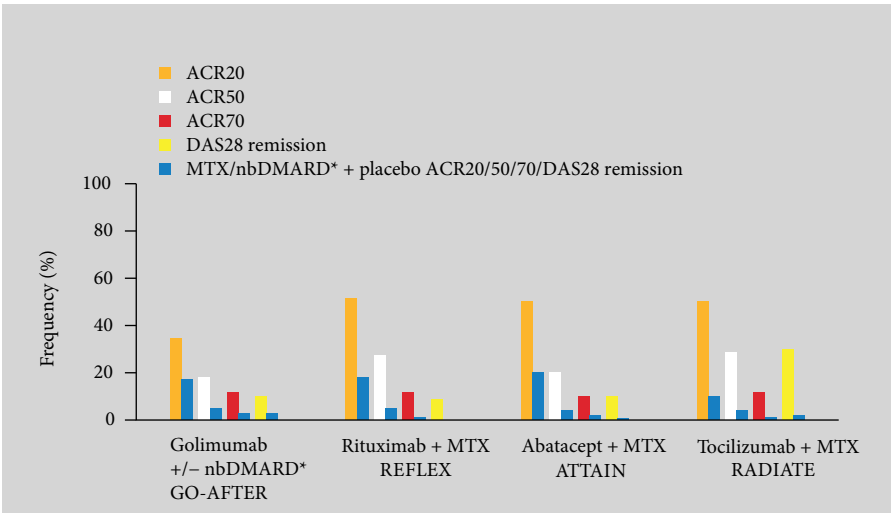


Figure 10.9 Efficacy of biological disease-modifying antirheumatic drug therapies at 6 months in patients with active rheumatoid arthritis despite previous tumor necrosis factor inhibitors. Results are shown for licensed dose groups. *In patients receiving nbDMARD at baseline this was continued (66% of patients received MTX, 30% did not receive MTX, sulfasalazine, or hydroxychloroquine). MTX, methotrexate; nbDMARD, nonbiologic disease-modifying antirheumatic drugs.

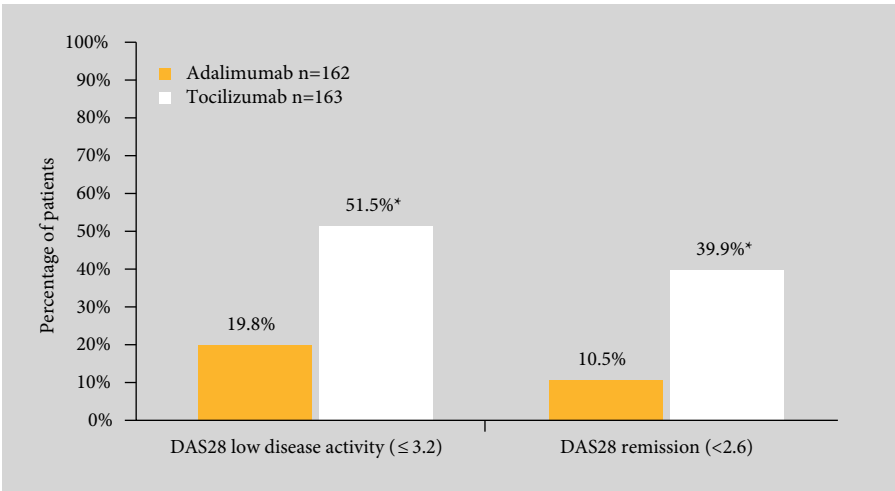


Figure 10.10 Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA). * $P < 0.0001$ versus adalimumab. DAS28, disease activity score for 28 joints. Reproduced with permission from Gabay et al [56] ©BMJ.

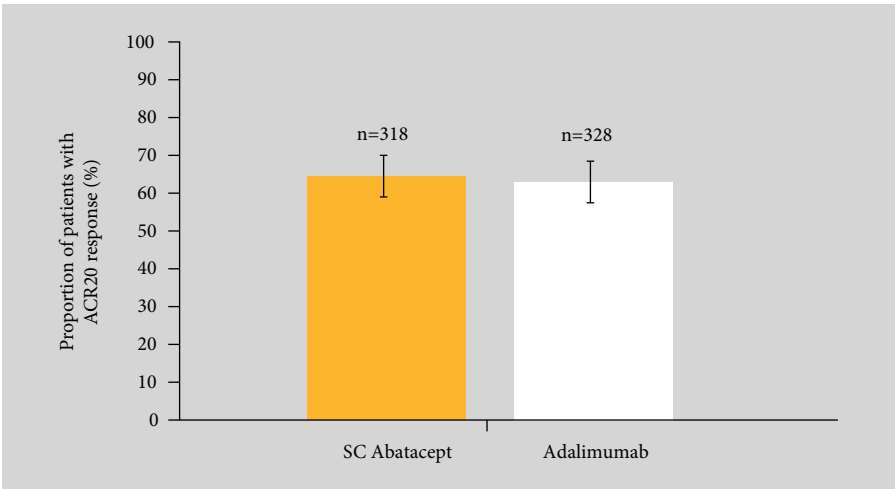


Figure 10.11 Rate of ACR20 response at 12 months in the AMPLE study: subcutaneous abatacept versus adalimumab, both in combination with methotrexate. Error bars represent 95% confidence intervals. ACR 20, American College of Rheumatology 20% improvement criteria; SC, subcutaneous. Reproduced with permission from Schiff et al [57] ©BMJ.

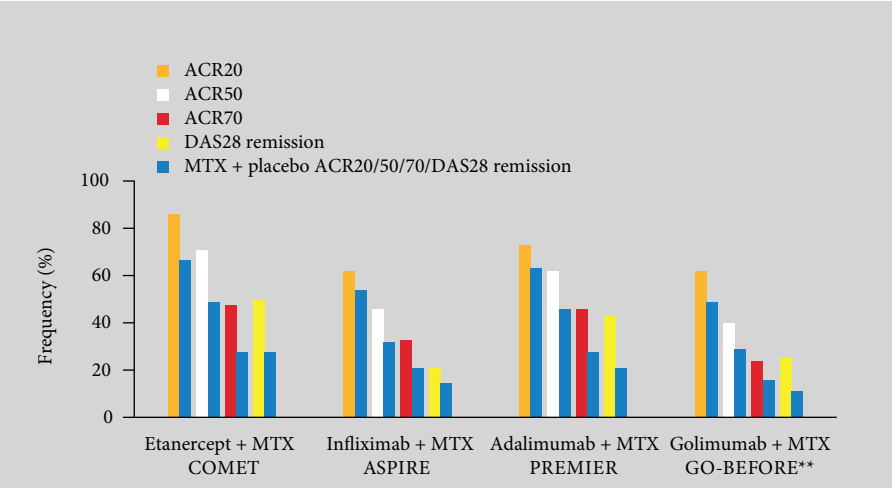


Figure 10.12 Efficacy of tumor necrosis factor inhibitors in combination with methotrexate at 1 year in methotrexate-naïve patients with early rheumatoid arthritis and poor prognostic factors. Results are shown for licensed dose groups. **Study duration in GO-BEFORE was 24 weeks (outcomes presented for study end). ACR 20/50/70, American College of Rheumatology 20%; 50%, and 70% improvement criteria; DAS28, disease activity score for 28 joints; MTX, methotrexate.

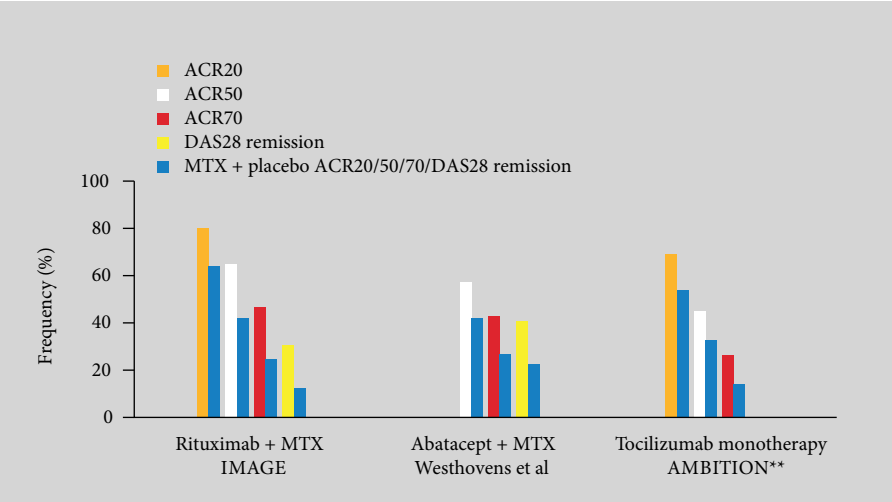


Figure 10.13 Efficacy of other biologic therapies at 1 year in methotrexate-naïve patients with rheumatoid arthritis and poor prognostic factors. Results are shown for licensed dose groups. **Study duration in AMBITION was 24 weeks (outcomes presented for study end). ACR 20/50/70, American College of Rheumatology 20%; 50%, and 70% improvement criteria; DAS28, disease activity score for 28 joints; MTX, methotrexate.

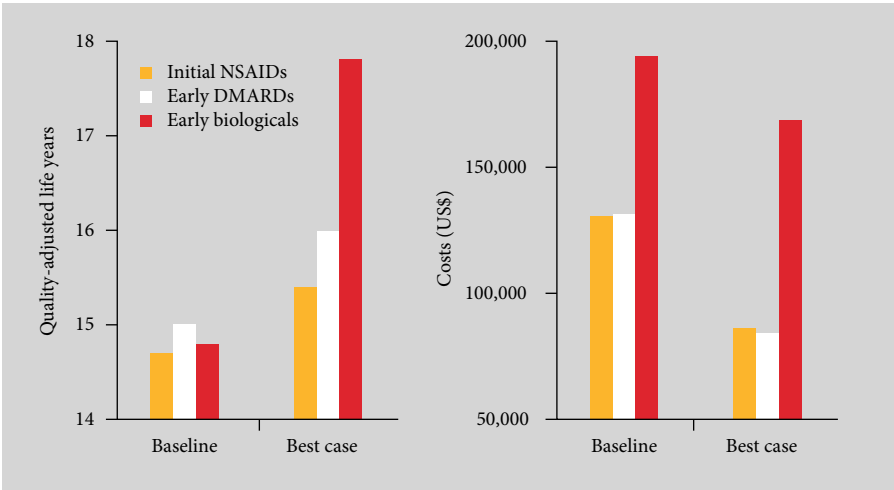


Figure 10.14 Cost-effectiveness analysis of treatment strategies in early rheumatoid arthritis. DMARD, disease-modifying antirheumatic drug; NSAID, nonsteroidal anti-inflammatory drug. Reproduced with permission from Scott et al [68] ©Lancet.

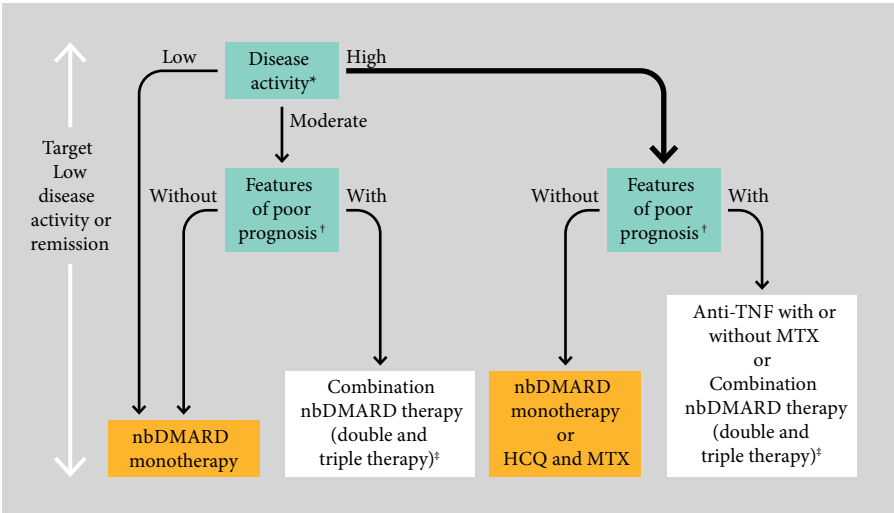


Figure 10.15 American College of Rheumatology (ACR) recommendations for the use of immunotherapies in early rheumatoid arthritis. *Disease activity assessed using a validated measure such as disease activity score (DAS); †Poor prognostic features include physical limitation (eg, Health Assessment Questionnaire score), extraarticular disease (eg, presence of rheumatoid nodules, rheumatoid arthritis [RA] vasculitis, Felty's syndrome), as well as rheumatoid factor/anti-citrullinated protein antibodies (ACPA) positive and radiographic erosions; ‡Combination nonbiologic disease-modifying antirheumatic drugs (nbDMARDs) therapy with two nbDMARDs (commonly including methotrexate [MTX]) and triple therapy (MTX, sulfasalazine, and hydroxychloroquine). Reproduced with permission from Singh et al [5] ©Wiley.

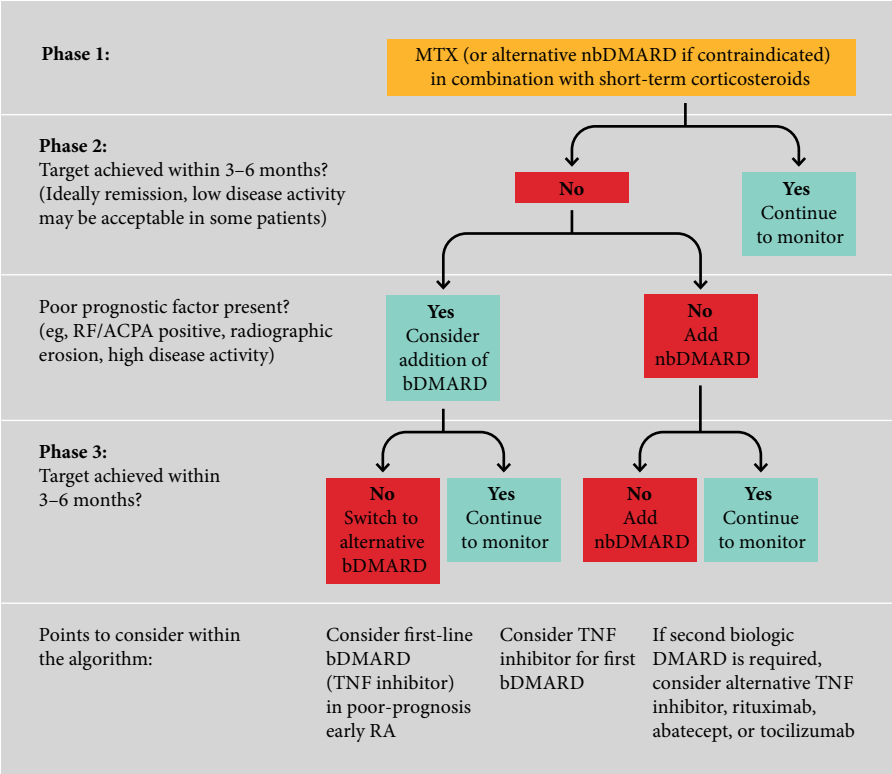


Figure 10.16 Schematic representation of the European League Against Rheumatism (EULAR) recommendations for the use of immunotherapies in early rheumatoid arthritis. bDMARD: biologic disease-modifying antirheumatic drug; MTX, methotrexate; nbDMARD, nonbiologic disease-modifying antirheumatic drug, TNF, tumor necrosis factor. Reproduced with permission from Smolen et al [22] ©BMJ.

	Methotrexate	Sulfasalazine	Hydroxychloroquine	Leflunomide
Pulmonary	Interstitial lung disease (ILD); may or may not be reversible, potentially causing pulmonary fibrosis (rare)	-	-	ILD: may or may not be reversible
Hematological	Myelosuppression (leukopenia and/or hypoplastic anemia and/or thrombocytopenia) Megaloblastic anemia	Hemolytic anemia in the presence of G6PD deficiency. Folate deficiency, megaloblastic anemia, granulocytopenia, immune thrombocytopenia	-	Myelosuppression (leukopenia and/or hypoplastic anemia and/or thrombocytopenia)
Hepatic	Elevated liver enzymes. Liver fibrosis is rare if liver function is monitored	Reduce dose in hepatic insufficiency. Elevated liver enzymes	-	Asymptomatic elevation of liver enzymes to fulminant hepatitis, liver cirrhosis, and failure
Renal	Contraindicated in renal disease	Reduce dose in renal insufficiency	Reduce dose in renal insufficiency.	Contraindicated in renal disease
Ophthalmological	-	-	Effects on the cornea (vortex keratopathy, no relationship to dose and usually reversible on cessation) and macular (may be associated with irreversible reduction in visual acuity)	-
Gastrointestinal	Nausea, diarrhea, ulcerative stomatitis	Nausea, diarrhea	Diarrhea	Nausea, diarrhea
Others	Alopecia, rash Rheumatoid nodules may worsen	Rash (may accompany fever and elevated liver enzymes). Avoid if previous hypersensitivity to sulfonamide drugs or salicylates	Rash, hyperpigmentation Myopathy (rare)	Alopecia. Skin reaction may be life-threatening (Stevens-Johnson syndrome and toxic epidermal necrolysis)
Pregnancy and lactation	Teratogenic	Relatively safe in pregnancy, use with caution in breast-feeding. Temporary oligospermia (men)	Relatively safe in pregnancy	Teratogenic. Avoid conception for 2 years after discontinuation or wash-out

Table 10.2 Safety considerations in the use of conventional disease-modifying antirheumatic drugs. G6PD, glucose-6-phosphate dehydrogenase deficiency.

	TNF inhibitors
Infection	Serious infection: 6 per 100 patient-years (calculated from pooled British Society of Rheumatology Biologics Register (BSRBR) data of patients receiving infliximab, etanercept, or adalimumab) [86] Opportunistic infections, reactivation of latent tuberculosis, and viral hepatitis reported. Screening and anti-tuberculous/antiviral therapy recommended. Risk of reactivation of latent tuberculosis appears higher with infliximab and adalimumab when compared to etanercept [87]
Malignancy	Risk of nonmelanotic skin cancer appears increased with etanercept, infliximab, or adalimumab in comparison to nbDMARDs (meta-analysis of prospective observational studies/registries; risk estimate 1.5 (95% CI; 1.2–1.8) [92]. Risk of all malignancies or lymphoma was not increased
Autoimmunity	Development of ANA and anti-dsDNA. Rare cases of autoimmune hepatitis, vasculitis, drug-induced systemic lupus erythematosus (occurring in approximately 0.2% of patients), and new onset of psoriasis
Pulmonary	Acute and occasionally fatal exacerbations of interstitial lung disease (ILD) have been reported. In patients with preexisting ILD in the BSRBR, etanercept, infliximab, and adalimumab were associated with a trend towards higher rate of mortality (23%) compared to DMARD therapy (21%), although not statistically significant [94]. Subsequent registry data have not confirmed this but caution is usually exercised in patients with clinically relevant ILD
Hematological	Cases of cytopenias have been reported
Cardiovascular	Contraindicated in type III and IV NYHA cardiac failure
Neurological/ demyelination	Reports of new onset or exacerbation of demyelinating disease
Hepatic	Rare reports of hepatic failure, including autoimmune hepatitis
Gastrointestinal	-
Injection site/ infusion reactions	Chimeric molecules (infliximab and rituximab) are associated with increased immunogenicity compared to humanised or fully human antibodies [98]
Pregnancy	There is a lack of evidence for the safety of biologics in pregnancy and lactation

Table 10.3 Safety considerations in the use of biologic therapies. AIR, autoimmunity and rituximab; ANA, anti-nuclear antibodies; anti-dsDNA, anti-double stranded DNA antibodies; CI, confidence interval; GI, gastrointestinal; NYHA, New York Heart Association; PML, progressive multifocal leukoencephalopathy.

Rituximab	Abatacept	Tocilizumab
Serious infection: 5 per 100 patient-years (AIR registry) [88]. Hepatitis B reactivation has been associated with rituximab (in oncology and hematology literature). Screening and appropriate treatment is recommended. Incidences of PML have been reported; although rare, this is a grave complication [89]	Serious infection: 5 per 100 patient-years (preliminary data of 16 serious infections in 682 patients) [88]	Serious infection: 5 per 100 patient-years (pooled data from clinical trials) [90]. Initial data from 112 patients treated in North Bavaria indicates rate may be increased in clinical practice (18 per 100 patient-years), but data from larger cohorts are awaited [91]
Limited long-term data. Pooled trial safety data are reassuring		
Development of psoriasis has been reported [93]	Autoimmune syndromes have been observed including vasculitis. New onset of psoriasis has been reported	-
The impact of rituximab in patients with preexisting ILD is unclear	Increased risk of exacerbations of chronic obstructive pulmonary disease (COPD) in clinical trials [95]	Unclear
Neutropenia (including late-onset). Hypogammaglobulinemia with rituximab associated with an increased risk of infection [96]	-	Neutropenia may be seen
Contraindicated in type IV NYHA cardiac failure	No clear signal but caution exercised	No clear signal but caution should be exercised
Phase I and II trials suggest rituximab may be effective in multiple sclerosis and neuromyelitis optica, however further evaluation is needed [97]. Reports of PML (see infection)	Reports of multiple sclerosis. Potential risk in worsening of demyelination in patients with preexisting disorders	Unclear
Hepatitis B reactivation	-	Elevations in liver transaminases
-	-	GI perforation (up to 3 per 1000 patient-years). Caution should be exercised in patients with a history that could increase risk, such as diverticulitis
Contraindicated in patients who have had a hypersensitivity reaction to infliximab		

Target	Drug	Mechanism of action
B-cell activating factor (BAFF)	Tabalumab (LY2127399)	Human monoclonal antibody against BAFF
Interleukin (IL)-17	LY2439821	Humanized monoclonal antibody against IL-17
	Secukinumab (AIN457)	Human monoclonal antibody against IL-17
Interleukin-20	NNC0109-0012	Human monoclonal antibody against IL-20
T-regulatory cells	BT-061	Humanized agonistic monoclonal antibody, activating T regulatory cells
GM-CSF	MORAb-022	Human monoclonal antibody against GM-CSF
	MOR103	Human monoclonal antibody against GM-CSF
	Mavrilumab	Human monoclonal antibody against GM-CSF receptor- α
Intracellular protein kinases	Tofacitinib (formerly tasocitinib)	Oral inhibitor of JAK 1 and 3
	Fostamatinib	Oral inhibitor of jaks and spleen tyrosine kinase
	Baricitinib	Oral inhibitor of JAK 1 and 2
	Masitinib	Oral inhibitor targeting stem cell factor receptor (c-kit) and PDGF receptor
Phosphodiesterases	Apremilast	Oral PDE4 inhibitor
	Revamilast	Oral PDE4 inhibitor

Table 10.4 Selection of prospective new immunotherapies with novel targets of action undergoing evaluation in rheumatoid arthritis clinical trials. GM-CSF, granulocyte-macrophage colony stimulating factor; JAK, Janus kinase; PDE4, phosphodiesterase-4 inhibitor; PDGF, platelet-derived growth factor.

References

1. Louie GH, Ward MM. Changes in the rates of joint surgery among patients with rheumatoid arthritis in California, 1983–2007. *Ann Rheum Dis*. 2010;69:868–871.
2. Sodergren A, Stegmayr B, Lundberg V, Ohman ML, Wallberg-Jonsson S. Increased incidence of and impaired prognosis after acute myocardial infarction among patients with seropositive rheumatoid arthritis. *Ann Rheum Dis*. 2007;66:263–266.
3. Westlake SL, Colebatch AN, Baird J, et al. Tumour necrosis factor antagonists and the risk of cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review. *Rheumatology*. 2011;50:518–531.
4. Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis*. 2010;69:631–637.
5. Singh JA, Furst DE, Bharat A, et al. 2012 Update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2012;64:625–639.
6. Furst DE, Keystone EC, Braun J, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2011. *Ann Rheum Dis*. 2012;71:i2–i45.
7. Curtis JR, Patkar N, Xie A, et al. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. *Arthritis Rheum*. 2007;56:1125–1133.
8. Askling J, Forell CM, Brandt L, et al. Time-dependent increase in risk of hospitalisation with infection among Swedish RA patients treated with TNF antagonists. *Ann Rheum Dis*. 2007;66:1339–1344.
9. Wolfe F, Caplan L, Michaud K, Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. *Arthritis Rheum*. 2006;54:628–634.
10. Dixon WG, Symmons DP, Lunt M, Watson KD, Hyrich KL, Silman AJ. Serious infection following anti-tumor necrosis factor alpha therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. *Arthritis Rheum*. 2007;56:2896–2904.
11. Galloway JB, Hyrich KL, Mercer LK, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology (Oxford)*. 2011;50:124–131.
12. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med*. 1999;340:253–259.
13. Keystone E, Van Der Heijde D, Mason D, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum*. 2008;58:3319–3329.
14. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. *Lancet*. 1999;354:1932–1939.
15. Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor α monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: The ARMADA trial. *Arthritis Rheum*. 2003;48:35–45.
16. Keystone E, Genovese MC, Klareskog L, et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. *Ann Rheum Dis*. 2010;69:1129–1135.
17. Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheum*. 2006;54:1390–1400.

18. Kremer JM, Genant HK, Moreland LW, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis. *Ann Intern Med.* 2006;144:865-876.
19. Maini RN, Taylor PC, Szechinski J, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum.* 2006;54:2817-2829.
20. Leombruno JP, Einarson TR, Keystone EC. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. *Ann Rheum Dis.* 2009;68:1136-1145.
21. Johnston A, Gudjonsson JE, Sigmundsdottir H, Runar Ludviksson B, Valdimarsson H. The anti-inflammatory action of methotrexate is not mediated by lymphocyte apoptosis, but by the suppression of activation and adhesion molecules. *Clin Immunol.* 2005;114:154-163.
22. Smolen JS, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis.* 2010;69:964-975.
23. Luqmani R, Hennell S, Estrach C, et al. British Society for Rheumatology and British Health Professionals in Rheumatology Guideline for the Management of Rheumatoid Arthritis (the first two years). *Rheumatology.* 2006;45:1167-1169.
24. Gaujoux-Viala C, Smolen JS, Landewé R, et al. Current evidence for the management of rheumatoid arthritis with synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis.* 2010;69:1004-1009.
25. Choy EHS, Smith C, Doré CJ, Scott DL. A meta-analysis of the efficacy and toxicity of combining disease-modifying antirheumatic drugs in rheumatoid arthritis based on patient withdrawal. *Rheumatology.* 2005;44:1414-1421.
26. Nam JL, Winthrop KL, Van Vollenhoven RF, et al. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. *Ann Rheum Dis.* 2010;69:976-986.
27. Smedegard G, Bjork J. Sulphasalazine: mechanism of action in rheumatoid arthritis. *Br J Rheumatol.* 1995;34(suppl 2):7-15.
28. Rahav G, Zylber-Katz E, Rachmilewitz D, Levy M. Relationship between the acetylator phenotype, plasma sulfapyridine levels and adverse effects during treatment with salicylazosulfapyridine in patients with chronic bowel diseases. *Isr J Med Sci.* 1990;26:31-34.
29. Katz SJ, Russell AS. Re-evaluation of antimalarials in treating rheumatic diseases: re-appreciation and insights into new mechanisms of action. *Curr Opin Rheumatol.* 2011;23:278-281.
30. Fox RI, Herrmann ML, Frangou CG, et al. Mechanism of action for leflunomide in rheumatoid arthritis. *Clin Immunol.* 1999;93:198-208.
31. Bos WH, Wolbink GJ, Boers M, et al. Arthritis development in patients with arthralgia is strongly associated with anti-citrullinated protein antibody status: a prospective cohort study. *Ann Rheum Dis.* 2010;69:490-494.
32. Nielen MMJ, Van Schaardenburg D, Reesink HW, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: A study of serial measurements in blood donors. *Arthritis Rheum.* 2004;50:380-386.
33. Cuthbert R, Parmar R, Nam J, et al. T-cell subsets dys-regulation and cytokines are predictive of RA pathogenesis in an ACPA-positive background. *Arthritis Rheum.* 62 (suppl 10):S455.
34. Confavreux CB, Chapurlat RD. Systemic bone effects of biologic therapies in rheumatoid arthritis and ankylosing spondylitis. *Osteoporos Int.* 2011;22:1023-1036.
35. Brennan F, Jackson A, Chantray D, Maini R, Feldmann M. Inhibitory effect of TNF- α antibodies on synovial cell interleukin-1 production in rheumatoid arthritis. *Lancet.* 1989;334:244-247.
36. Buch MH, Bingham SJ, Bryer D, Emery P. Long-term infliximab treatment in rheumatoid arthritis: subsequent outcome of initial responders. *Rheumatology (Oxford).* 2007;46:1153-1156.
37. Mease, P. *Atlas of Psoriatic Arthritis*. London, UK: Current Medicine Group; 2005.
38. Wolf D, Mahadevan U. Certolizumab Pegol use in pregnancy: low levels detected in cord blood (abstract). *Arthritis Rheum.* 2010;62(suppl10):299.

39. Porter C, Kopotsha T, Smith B, Nesbitt A, Urbaniak S, Armstrong-Fisher S. No significant transfer of certolizumab pegol compared with IgG in the perfused human placenta in vitro (abstract). *Ann Rheum Dis.* 2010;69 (suppl 3):210.
40. Nesbitt A, Fossati G, Bergin M, et al. Mechanism of action of certolizumab pegol (CDP870): In vitro comparison with other anti-tumor necrosis factor α agents. *Inflamm Bowel Dis.* 2007;13:1323-1332.
41. Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: A comprehensive review. *Pharmacol Ther.* 2008;117:244-279.
42. Taylor PC. Pharmacology of TNF blockade in rheumatoid arthritis and other chronic inflammatory diseases. *Current Opin Pharmacol.* 2010;10:308-315.
43. Taylor RP, Linderforfer MA. Drug Insight: the mechanism of action of rituximab in autoimmune disease – the immune complex decoy hypothesis. *Nat Clin Pract Rheumatol.* 2007;3:86-95.
44. Dass S, Rawstron AC, Vital EM, Henshaw K, McGonagle D, Emery P. Highly sensitive B cell analysis predicts response to rituximab therapy in rheumatoid arthritis. *Arthritis Rheum.* 2008;58:2993-2999.
45. Ruderman EM, Pope RM. Drug insight: abatacept for the treatment of rheumatoid arthritis. *Nat Clin Pract Rheumatol.* 2006;2:654-660.
46. Mihara M, Tan I, Chuzhin Y, et al. CTLA4Ig inhibits T cell-dependent B-cell maturation in murine systemic lupus erythematosus. *J Clin Invest.* 2000;106:91-101.
47. Kishimoto T. Interleukin-6: discovery of a pleiotropic cytokine. *Arthritis Res Ther.* 2006; 8(suppl. 2):S2.
48. Muraguchi A, Hirano T, Tang B, et al. The essential role of B cell stimulatory factor 2 (BSF-2/IL-6) for the terminal differentiation of B cells. *J Exp Med.* 1988;167:332-344.
49. Lotz M, Jirik F, Kabouridis P, et al. B cell stimulating factor 2/interleukin 6 is a costimulant for human thymocytes and T lymphocytes. *J Exp Med.* 1988;167:1253-1258.
50. Smolen JS, Han C, Bala M, et al. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: A detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. *Arthritis Rheum.* 2005;52:1020-1030.
51. Dougados M, Huizinga T, Sheeran T, et al. Tocilizumab (TCZ) plus methotrexate (MTX) does not have superior clinical efficacy to TCZ alone in RA patients with inadequate response to MTX: 24-week results of the ACT-RAY study (abstract). *Ann Rheum Dis.* 2011;70:73.
52. Smolen JS, Kay J, Doyle MK, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. *Lancet.* 2009;374:210-221.
53. Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum.* 2006;54:2793-2806.
54. Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis.* 2008;67:1516-1523.
55. Genovese MC, Becker J-C, Schiff M, et al. Abatacept for Rheumatoid Arthritis Refractory to Tumor Necrosis Factor α Inhibition. *N Eng J Med.* 2005;353:1114-1123.
56. Gabay C, Emery P, Van Vollenhoven R, et al. Tocilizumab (TCZ) monotherapy is superior to adalimumab (ADA) monotherapy in reducing disease activity in patients with rheumatoid arthritis (RA): 24-week data from the phase 4 ADOCTA trial. *Ann Rheum Dis.* 2012;71(suppl 3):152.
57. Schiff M, Fleischmann R, Weinblatt M, et al. Abatacept versus adalimumab on background methotrexate in RA: one year results from the AMPLE study. *Ann Rheum Dis.* 2012;71(suppl 3):60.
58. St Clair EW, Van Der Heijde D, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum.* 2004;50:3432-3443.
59. Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum.* 2006;54:26-37.

60. Emery P, Breedveld FC, Hall S, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet*. 2008;372:375-382.
61. Emery P, Fleischmann RM, Moreland LW, et al. Golimumab, a human anti-tumor necrosis factor α monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naïve patients with active rheumatoid arthritis: Twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. *Arthritis Rheum*. 2009;60:2272-2283.
62. Emery P, Kvein TK, Combe B, et al. Very early (<4 months) treatment with combination etanercept and methotrexate produces significantly better remission rates: results from the COMET study. *Ann Rheum Dis*. 2010;69:57.
63. Emery P, Genovese MC, Van Vollenhoven R, Sharp JT, Patra K, Sasso EH. Less radiographic progression with adalimumab plus methotrexate versus methotrexate monotherapy across the spectrum of clinical response in early rheumatoid arthritis. *J Rheumatol*. 2009;36:1429-1441.
64. Klareskog L, Van Der Heijde D, De Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet*. 2004;363:675-681.
65. Tak PP, Rigby WF, Rubbert-Roth A, et al. Inhibition of joint damage and improved clinical outcomes with rituximab plus methotrexate in early active rheumatoid arthritis: the IMAGE trial. *Ann Rheum Dis*. 2011;70:39-46.
66. Westhovens R, Robles M, Ximenes AC, et al. Clinical efficacy and safety of abatacept in methotrexate-naïve patients with early rheumatoid arthritis and poor prognostic factors. *Ann Rheum Dis*. 2009;68:1870-1877.
67. Jones G, Sebba A, Gu J, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. *Ann Rheum Dis*. 2010;69:88-96.
68. Scott DL, Wolfe F, Huizinga TWJ. Rheumatoid arthritis. *Lancet*. 376:1094-1108.
69. Bejarano V, Conaghan PG, Quinn MA, Saleem B, Emery P. Benefits 8 years after a remission induction regime with an infliximab and methotrexate combination in early rheumatoid arthritis. *Rheumatology*. 2010;49:1971-1974.
70. Quinn MA, Conaghan PG, O'Connor PJ, et al. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2005;52:27-35.
71. Saleem B, Keen H, Goeb V, et al. Patients with RA in remission on TNF blockers: when and in whom can TNF blocker therapy be stopped? *Ann Rheum Dis*. 2010;69:1636-1642.
72. Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet*. 2004;364:263-269.
73. Verstappen SMM, Jacobs JWG, Van Der Veen MJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). *Ann Rheum Dis*. 2007;66:1443-1449.
74. Van Vollenhoven RF, Ernestam S, Geborek P, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. *Lancet*. 2009;374:459-466.
75. Goekoop-Ruiterman YPM, De Vries-Bouwstra JK, Allaart CF, et al. Comparison of treatment strategies in early rheumatoid arthritis. *Ann Intern Med*. 2007;146:406-415.
76. Moreland LW, O'Dell JR, Paulus HE, et al. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early, aggressive rheumatoid arthritis. *Arthritis Rheum*. 2012; 64:2824-2835.

77. Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis *Lancet*. 1997;350:309-318.
78. Möttönen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. *Lancet*. 1999;353:1568-1573.
79. Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2008;59:762-784.
80. Dawson TM, Starkebaum G, Wood BL, Willkens RF, Gown AM. Epstein-Barr virus, methotrexate, and lymphoma in patients with rheumatoid arthritis and primary Sjögren's syndrome: case series. *J Rheumatol*. 2001;28:47-53.
81. European Medicines Agency (EMA). EMA Public Statement on Leflunomide (Arava) - severe and serious hepatic reactions. EMA website. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/08/news_detail_001088.jsp&mid=WC0b01ac058004d5c1. Updated October 25, 1999. Accessed March 6, 2015.
82. Marmor MF, Kellner U, Lai TYY, Lyons JS, Mieler WF. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. *Ophthalmology*. 2011;118:415-422.
83. Smitten AL, Simon TA, Hochberg MC, Suissa S. A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. *Arthritis Res Ther*. 2008;10:R45.
84. Watson KD, Dixon WG, Hyrich KL, Lunt M, Symmons DP, Silman AJ. Influence of anti-TNF therapy and previous malignancy on cancer incidence in patients with rheumatoid arthritis (RA): results from the BSR biologics register (abstract). *Ann Rheum Dis*. 2006;65:512.
85. Strangfeld A, Hierse F, Rau R, et al. Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT. *Arthritis Res Ther*. 2010;12:R5.
86. Dixon WG, Symmons DPM, Lunt M, Watson KD, Hyrich KL, Silman AJ. Serious infection following anti-tumor necrosis factor α therapy in patients with rheumatoid arthritis: Lessons from interpreting data from observational studies. *Arthritis Rheum*. 2007;56:2896-2904.
87. Dixon WG, Hyrich KL, Watson KD, et al. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). *Ann Rheum Dis*. 2010;69:522-528.
88. Mariette X, Gottenberg J-E, Ravaud P, Combe B. Registries in rheumatoid arthritis and autoimmune diseases: data from the French registries. *Rheumatology*. 2011;50:222-229.
89. Buch MH, Smolen JS, Betteridge N, et al. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2011;70:909-920.
90. Schiff MH, Kremer JM, Jahreis A, Vernon E, Isaacs JD, Van Vollenhoven RF. Integrated safety in tocilizumab clinical trials. *Arthritis Res Ther*. 2011;13:R141.
91. Lang VR, Englbrecht M, Rech J, et al. Risk of infections in rheumatoid arthritis patients treated with tocilizumab. *Rheumatology*. 2012;51:852-857.
92. Mariette X, Matucci-Cerinic M, Pavelka K, et al. Malignancies associated with tumour necrosis factor inhibitors in registries and prospective observational studies: a systematic review and meta-analysis. *Ann Rheum Dis*. 2011;70:1895-1904.
93. Dass S, Vital EM, Emery P. Development of psoriasis after B cell depletion with rituximab. *Arthritis Rheum*. 2007;56:2715-2718.
94. Dixon WG, Hyrich KL, Watson KD, et al. Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis-associated interstitial lung disease: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis*. 2010;69:1086-1091.

95. Hadjinicolaou AV, Nisar MK, Bhagat S, Parfrey H, Chilvers ER, Östör AJK. Non-infectious pulmonary complications of newer biological agents for rheumatic diseases – a systematic literature review. *Rheumatology*. 2011;50: 2297-2305.
96. Gottenberg JE, Ravaud P, Bardin T, et al. Risk factors for severe infections in patients with rheumatoid arthritis treated with rituximab in the autoimmunity and rituximab registry. *Arthritis Rheum*. 2010;62: 2625-2632.
97. Hawker K, O'Connor P, Freedman MS et al. Rituximab in patients with primary progressive multiple sclerosis: Results of a randomized double-blind placebo-controlled multicenter trial. *Ann Neurol*. 2009;66: 460-471.
98. Hwang WYK, Foote J. Immunogenicity of engineered antibodies. *Methods*. 2005;36:3-10.
99. Genovese MC, Mociran E, Biagini M, Bojin S, Sloan-Lancaster J. Phase 2 study of safety and efficacy of a novel anti-BAFF monoclonal antibody, in patients with RA treated with methotrexate [abstract]. *Arthritis Rheum*. 2009;60 (suppl 10):1923.
100. Genovese MC, Van Den Bosch F, Roberson SA, et al. LY2439821, a humanized anti-interleukin-17 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: a phase I randomized, double-blind, placebo-controlled, proof-of-concept study. *Arthritis Rheum*. 2010;62:929-939.
101. Genovese MC, Durez P, Richards HB, et al. Efficacy and safety of secukinumab in patients with rheumatoid arthritis: a phase II, dose-finding, double-blind, randomised, placebo controlled study. *Ann Rheum Dis*. 2013;72:863-869.
102. Šenolt L, Göthberg M, Valencia X, Dokoupilová E. Efficacy and safety of NNC0109-0012 (anti-IL-20 mAb) in patients with rheumatoid arthritis: results from a phase 2a trial [abstract]. *Ann Rheum Dis*. 2012;71:152.
103. Burmester GR, Feist E, Sleeman MA, Wang B, White B, Magrini F. Mavrilimumab, a human monoclonal antibody targeting GM-CSF receptor- α , in subjects with rheumatoid arthritis: a randomised, double-blind, placebo-controlled, Phase I, first-in-human study. *Ann Rheum Dis*. 2011;70:1542-1549.
104. Rudnev A, Ragavan S, Trollmo C, et al. Selective activation of naturally occurring regulatory T cells by the monoclonal antibody BT-061. Markers of clinical activity and early phase II results in patients with rheumatoid arthritis (abstract). *Arthritis Rheum*. 2010;62:1125.
105. Van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or Adalimumab versus Placebo in Rheumatoid Arthritis. *N Eng J Med*. 2012;367:508-519.
106. Weinblatt ME, Kavanaugh A, Burgos-Vargas R, et al. Treatment of rheumatoid arthritis with a syk kinase inhibitor: A twelve-week, randomized, placebo-controlled trial. *Arthritis Rheum*. 2008;58:3309-3318.
107. Tebib J, Mariette X, Bourgeois P, et al. Masitinib in the treatment of active rheumatoid arthritis: results of a multicentre, open-label, dose-ranging, Phase 2a study. *Arthritis Res Ther*. 2009;11:R95.
108. Genovese MC, Kavanaugh A, Weinblatt ME et al. An oral Syk kinase inhibitor in the treatment of rheumatoid arthritis: a three-month randomized, placebo-controlled, phase II study in patients with active rheumatoid arthritis that did not respond to biologic agents. *Arthritis Rheum*. 2011;63:337-345.
109. Mccann F, Palfreeman A, Andrews M, et al. Apremilast, a novel PDE4 inhibitor, inhibits spontaneous production of tumour necrosis factor-alpha from human rheumatoid synovial cells and ameliorates experimental arthritis. *Arthritis Res Ther*. 2010;12:R107.

11 Rituximab

Ed Vital

B-cell development and differentiation

B cells develop from progenitor cells in bone marrow. They are released into the circulation as transitional B cells, and then become mature naïve B cells. If they encounter their cognate antigen they undergo activation, may receive T-cell help in germinal centers, and then undergo class switching and affinity maturation, ultimately resulting in the generation of memory B cells and plasmablasts. The latter are short-lived in peripheral blood but if they can find a niche in bone marrow or inflammatory tissue (such as the rheumatoid arthritis [RA] synovium), then they may become short- or long-lived plasma cells that produce large quantities of secreted antibody for months to years (Figure 11.1) [1–6]. In some circumstances they may be activated and differentiate without T-cell help or class switching.

B cells in rheumatoid arthritis

B cells were hypothesized to be involved in the earliest models of RA once rheumatoid factor (RF) had been identified as a disease-associated autoantibody. However, the relationship of antibody to disease was not 1:1 and other evidence pointed to a crucial role for presentation of major histocompatibility complex (MHC)-bound antigen, T-cell activation and synovial infiltration and macrophage and fibroblast-derived cytokines [7]. A fresh model based on RF was proposed again by Edward and Cambridge in 1998 and was the initial rationale for trials of B-cell depleting therapy (Figure 11.2) [8].

Once B-cell depletion came to be used clinically, later models emphasized the non-anti-body roles of B cells (Figure 11.3) [9]. Although B-cell depletion is known to be effective [10], there are unanswered questions regarding the precise contribution of B cells to RA and the mechanism of action of B-cell depleting therapy.

B-cell killing with rituximab

Rituximab is a monoclonal antibody specific for CD20 that results in B-cell killing. It was originally developed to treat B cell malignancies but has since been used in autoimmune diseases, most commonly rheumatoid arthritis, systemic lupus erythematosus (SLE), and antineutrophil cytoplasmic autoantibody (ANCA)-vasculitis. There are three possible mechanisms of cell killing for anti-CD20 antibodies:

- antibody-dependent cell-mediated cytotoxicity (ADCC);
- complement-dependent cytotoxicity (CDC); and
- induction of apoptosis.

However, only indirect evidence suggests which is most important in vivo (Figure 11.4) [11].

Efficacy of rituximab in rheumatoid arthritis

Initial evidence for the efficacy of B-cell depletion in rheumatoid arthritis was case series of combination regimes that included cyclophosphamide or methotrexate and high dose oral and intravenous corticosteroids. Hence, initial randomized controlled trials (RCTs), such as the study conducted by Edwards et al and the DANCER study in RA, were intended to demonstrate the efficacy of the rituximab (RTX) component of such regimes, the most appropriate dose, and the most appropriate combination immunosuppressant required (if any) [11,12]. These trials showed that intravenous corticosteroids reduce infusion reactions; additional oral corticosteroids confer no additional long-term benefit; and that combination with methotrexate is more effective than cyclophosphamide or rituximab monotherapy [11,12]. The REFLEX trial confirmed the value of an intravenous corticosteroids-methotrexate-rituximab regime, as well as efficacy in radiographic endpoints, and led to a license for rituximab [13].

Trials that included semiannual retreatment generally led to stable control of disease activity with no apparent worsening of safety [14–16]. However, a comparison of fixed retreatment and retreatment on demand can only be made indirectly between trials that recruited different patient populations, and this must be interpreted carefully [17]. The RCT evidence for the efficacy of rituximab in RA is summarized in Table 11.1.

B-cell depletion in peripheral blood

Initial reports seemed to indicate universal, complete B-cell depletion in all patients followed by repopulation after 6 months or longer [10]. Subsequent studies showed that depletion and repopulation varied between different B cell subsets more than initially believed (Figure 11.5) [18]. High numbers of plasmablasts at baseline and day 15 were associated with inferior clinical response.

The presence of plasmablasts in isolation in peripheral blood suggests continuing B cell activity in other sites, such as lymphoid tissue (Figure 11.6). However, the exact function of these cells has not yet been elucidated. One study suggested they were mucosally derived and distinct from the T cell-dependent disease-associated B cell activity thought to contribute to RA [19]. However, recent data have indicated that they produce RA-associated autoantibodies and their numbers are associated with range of antibodies expressed [13]. Similarly, in SLE, plasmablast numbers are associated with range of autoantibodies and their early repopulation is strongly predictive of relapse [20].

B-cell depletion in the synovium

The RA synovium is a site of B-cell activity, with lymphoid infiltrates in all patients, and the formation of lymphoid aggregates or germinal center-like structures in some. Rituximab is able to deplete B cells in the RA synovium efficiently, as shown in Figure 11.7 [21,22]. Reduction of plasma cell numbers is less consistent and some data indicate an association of higher pre- and post-treatment plasma cell numbers with response, although there is inconsistency between studies (Figures 11.8 and 11.9) [21,22].

Retreatment with rituximab for nonresponse

Given the association between increased pre- and post-treatment B lineage cell numbers and nonresponse, the use of further cycles of rituximab seems logical in patients who fail to respond to the first. Further B-cell depletion may increase killing of resistant B cells or allow the attrition of plasma cells that outlive the period of B-cell depletion and studies support this strategy (Figure 11.10) [23].

Antibody status and response to rituximab

There is general agreement that in RA response to rituximab is better in patients who are positive for autoantibodies (Figures 11.11 and 11.12) [24,25]. Data on titers of antibodies are

less clear. These studies found no link between titre of antibodies and response, but some have reported higher titres of immunoglobulin M-anticyclic citrullinated protein antibodies (IgM-ACPA) in patients who did not achieve European League Against Rheumatism (EULAR) 'good response' [21]. What has not been shown is a link between reduction in autoantibody titer and clinical response. Titers of RF and ACPA reduce after rituximab therapy, but only partially, and to a similar degree in clinical responders and non-responders. Autoantibody tests, therefore, seem able to identify patients with non-B-cell-mediated inflammatory arthritis by their negativity at baseline, but other than this have limited value in explaining the mechanism of action of therapeutic B-cell depletion.

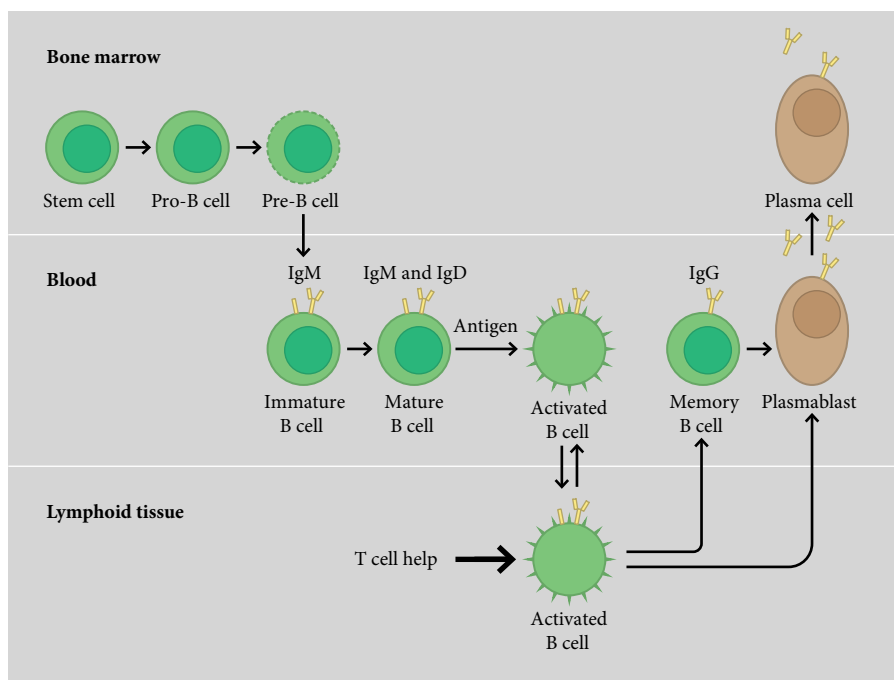


Figure 11.1 B-cell development, activation, and differentiation. The maturation and activation of the B lineage, from progenitors in bone marrow to short- and long-lived plasma cells. CD20 is expressed from Pre-B cells to memory B cells, but not on plasmablasts or plasma cells. The range of expression of CD20 is ideal as a target for the treatment of B-cell malignancies because stem cells and plasma cells are spared from depletion. In the treatment of autoimmune disease, the benefits of this range of expression are somewhat less clear because plasma cells and their antibodies may have a role in causing inflammation. Furthermore, experience has shown that relapse almost always occurs following a response to rituximab in autoimmune disease, so repeat cycles of treatment are used, resulting in long-term B-cell depletion. Rapid repopulation may, therefore, be undesirable in long-term maintenance of response, and repeat cycles may lead to greater attrition of plasma cells than a single cycle of therapy. Ig, immunoglobulin.

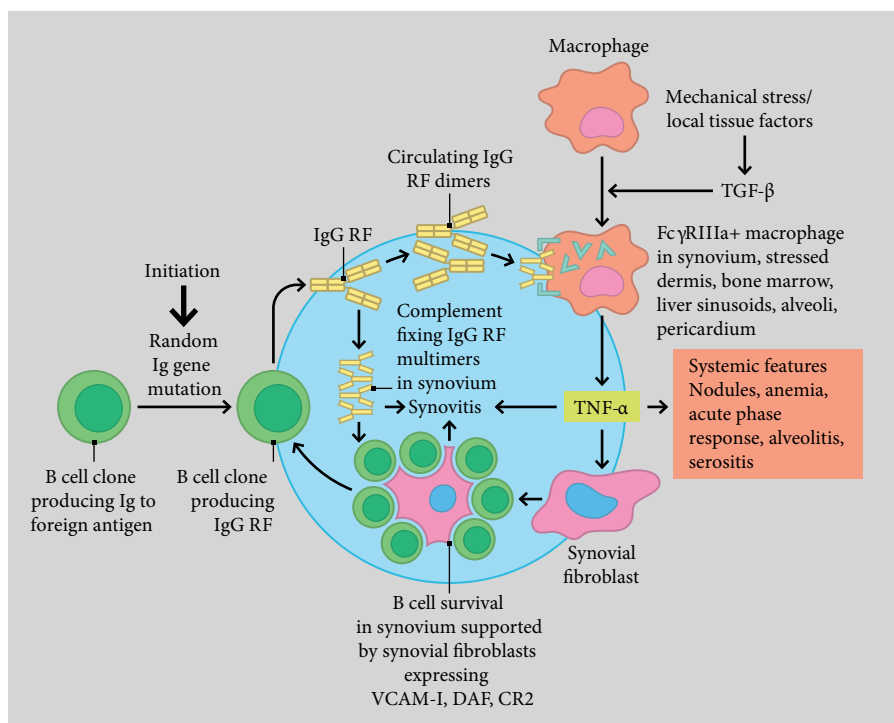


Figure 11.2 The Edwards and Cambridge RF-based hypothesis of rheumatoid arthritis. In this model, immunoglobulin G-rheumatoid factor (IgG RF) forms self-associating small immune complexes that are able to evade clearance by complement in the circulation but may trigger inflammation in the synovium via Fcγ receptors. The pathology of the disease appears to match the distribution of the Fcγ receptor IIIa (FcγRIIIa). RF-secreting B cells are able to proliferate without the help of a similarly autoreactive T cell by presenting RF-bound foreign antigen to nonautoreactive T cells. Hence, this model proposed a reason for the break in immune tolerance, as well as a mechanism for RF to lead to inflammation. CR2, complement receptor 2; DAF, decay-accelerating factor; TGF α/β , transforming growth factor alpha/beta; TNF- α , tumor necrosis factor alpha; VCAM, vascular cell adhesion protein. Reproduced with permission from Edwards and Cambridge [8] ©Oxford University Press.

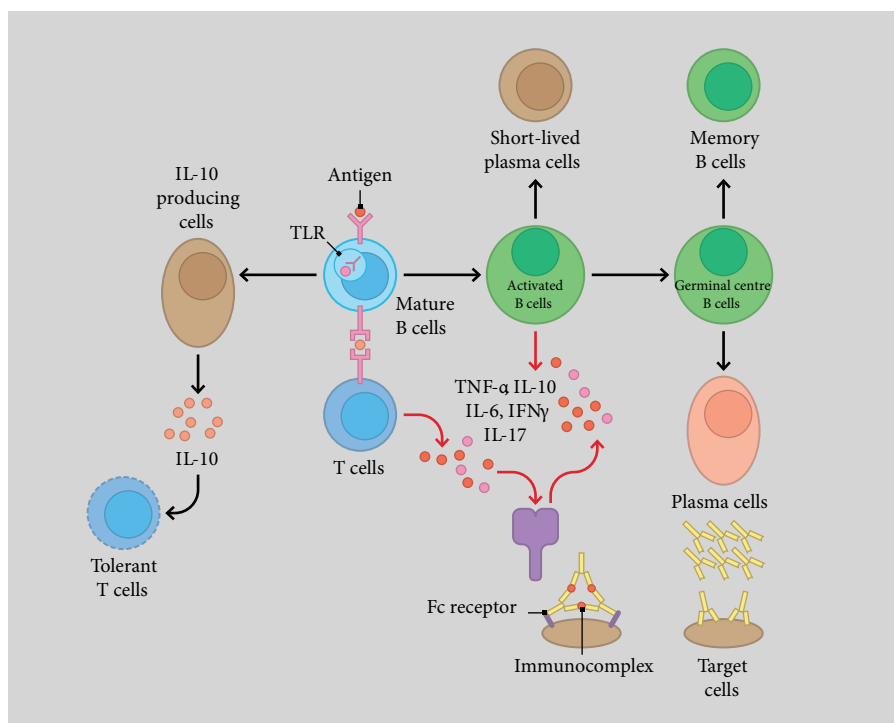


Figure 11.3 Later models emphasize the nonantibody roles of B cells. B cells are highly efficient as antigen-presenting cells and in some contexts may have a unique role in activating T cells that cannot be substituted by other types of antigen presenting cell. They may also secrete inflammatory cytokines. Initial experience with rituximab did not find that clearance of rheumatoid factor (RF) was usually achieved, nor was this necessary for clinical response. Later evidence had demonstrated the importance of another class of antibodies (anticitrullinated peptide antibodies), which are linked to the genetic major histocompatibility complex (MHC) association of rheumatoid arthritis. IFN, interferon; IL, interleukin; TLR, toll-like receptor. Reproduced with permission from Mauri and Ehrenstein [9] ©BioMed Central.

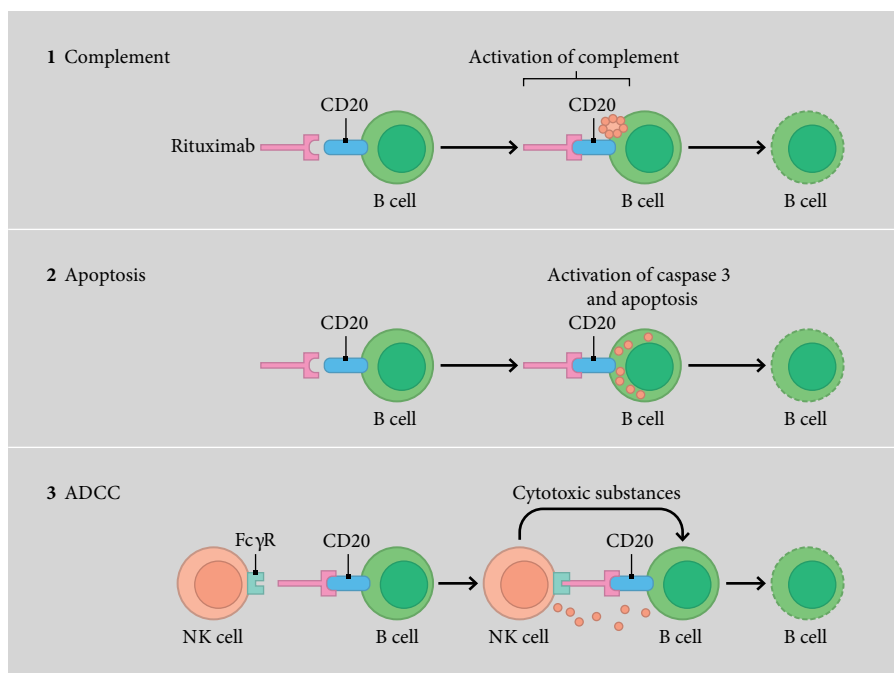


Figure 11.4 Mechanisms of B-cell killing. Antibody-dependent cell mediated cytotoxicity (ADCC) is believed to be the most important mechanism. ADCC mediated by Fcγ receptor (FcγR)-bearing effector cells (natural killer [NK] cells or monocytes/macrophages) has been demonstrated in animal models and in patients treated with rituximab. FcγRIIIa polymorphisms have been associated with increased rituximab binding by NK cells and monocytes and increased killing by ADCC. Such polymorphisms have been shown to influence B-cell killing and overall survival after rituximab treatment of patients with Non-Hodgkin's lymphoma [1]. A study of 12 patients with systemic lupus erythematosus (SLE) suggested that the degree of B-cell depletion by rituximab in SLE was also associated with FcγRIIIa genotype [2]. Several lines of evidence support a role for complement-dependent cytotoxicity (CDC) as a mechanism of action of rituximab. The susceptibility of various B-cell malignancies to CDC in vitro is consistent with the resistance of each malignancy to rituximab in vivo. C1q deficient mice exhibit impaired B-cell killing [3]. Complement consumption has been observed in patients with B-NHL during treatment with rituximab [4]. The efficiency of CDC may depend on the proximity of the monoclonal antibody target epitope to the cell surface, as is the case for anti-CD52 [5]. Differential migration of antibody-bound CD20 into lipid rafts may influence the degree of CDC. On this basis, anti-CD20 antibodies have been classified into two types, based upon their relative abilities to induce translocation of antibody-bound CD20 into insoluble lipid rafts: type 1 antibodies induce translocation and are potent inducers of complement, whereas type 2 antibodies do not induce translocation. Both type 1 and type 2 antibodies can trigger ADCC, but type 2 antibodies may induce apoptosis more efficiently. Rituximab is classified as a type 1 antibody. Anti-CD20 antibodies may induce apoptosis directly in vitro. When patients with B-cell chronic lymphocytic leukemia (B-CLL) were treated with rituximab, the degree of B-cell killing correlated with expression of caspase-3 and caspase-9, both of which are enzymes involved in the process of apoptosis. However, there is less evidence to support this mechanism. Reproduced with permission from Hochberg et al [6] ©Elsevier.

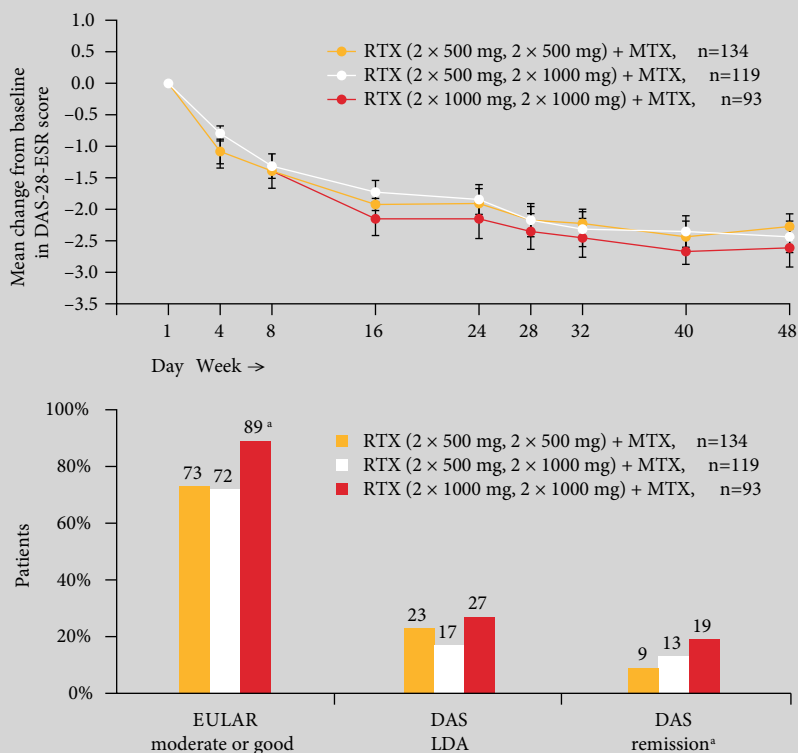


Figure 11.5 Dose intervals of rituximab (RTX) and methotrexate (MTX). Evidence on dose of rituximab and re-treatment interval is complex. Clinical response rates were numerically better at the 2×1000 mg dose in the DANCER study [12] compared to a 2×500 mg dose, and EULAR response rates were significantly better in MIRROR [14] – both in established rheumatoid arthritis (RA) that is resistant to methotrexate and usually also tumor necrosis factor (TNF)-blocking therapies. The SERENE [15] and IMAGE [16] trials in earlier RA populations did not demonstrate any difference in clinical outcomes between doses in earlier RA populations, although there was a difference in radiographic outcomes. Collectively, these trials indicate that a 2×500 mg dose of rituximab is effective, but there are some advantages to a 2×1000 mg dose, especially in the first cycle of treatment. DAS, disease activity score; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; LDA, low disease activity.

Study	Population	Randomization	Endpoints
Edwards et al.	MTX-IR RF-positive	1: MTX (n=40) 2: RTX1000 mg (n=40) 3: RTX1000 + CyP (n=41) 4: RTX1000 + MTX (n=40) All groups had PO-CS and IV-CS	1: ACR50 week 24 2: DAS28, EULAR and ACR responses at 24 and 48 weeks
DANCER	MTX-IR or TNF-IR RF/CCP positive or negative	1: Placebo 2: Placebo + IV-CS 3: Placebo + IV-CS + PO-CS 4: RTX500 mg 5: RTX500 + IV-CS 6: RTX500 + IV-CS + PO-CS 7: RTX1000 8: RTX1000 + IV-CS 9: RTX1000 + IV-CS + PO-CS All groups had MTX Total n=465 Retreatment on relapse	1: ACR20 week 24 2: DAS28, EULAR and ACR responses week 24, HAQ, FACIT-F, safety, Ig, HACA
REFLEX	TNF-IR RF/CCP positive or negative	1: Placebo + MTX (n=209) 2: RTX1000 + MTX (n=311) All groups had PO-CS and IV-CS Retreatment on relapse	1: ACR20 week 24 2: DAS28, EULAR and ACR responses week 24 Other: HAQ, FACIT-F, radiographic, safety
SERENE	MTX-IR RF/CCP positive or negative	1: Placebo + MTX 2: RTX500 + MTX 3: RTX1000 + MTX Retreatment from week 24 unless in remission	1: ACR20 week 24 2: DAS28, EULAR and ACR responses, HAQ, SF36, FACIT-F
MIRROR	MTX-IR or TNF-IR RF/CCP positive or negative	1: RTX500 then RTX500 2: RTX500 then RTX1000 3: RTX1000 then RTX1000 Treatment at 0 and 24 weeks in all patients All patients received MTX	1: ACR20 week 48 2: DAS28, EULAR and ACR responses, HAQ, SF36, FACIT-F
IMAGE	MTX-naïve RF negative patients needed erosions to enroll	1: Placebo + MTX 2: RTX500 + MTX 3: RTX1000 + MTX Retreatment from week 24 unless in remission	1: change mTSS week 52 Other: Major Clinical Response (maintenance of ACR70 >6 months). DAS28, EULAR and ACR responses, HAQ, SF36, FACIT-F

Table 11.1 Summary of rituximab randomized controlled trials. These trials have clearly established that a regime based on rituximab and methotrexate is more effective than methotrexate alone, and that additional oral corticosteroids or intravenous cyclophosphamide are not required. However, the evidence regarding the best dose and retreatment interval is less clear from these studies, and indeed may differ at different times or in different patient groups. ACR50, American College of Rheumatology 50% improvement; AE, adverse event; CCP, cyclic citrullinated protein; CS, corticosteroid; CyP, cyclophosphamide; DAS28, disease activity score in 28 joints;

Key findings	Ref
All RTX arms superior to MTX at 6 months. Only arms 3 and 4 significantly superior at 12 months B cells depleted in all RTX groups for 24 weeks RF reduced; total Igs remained stable	[11]
All RTX arms superior to placebo Time to best response 12–24 weeks Numerically higher ACR70 and EULAR-Good in RTX1000 groups vs. RTX500. CS did not influence efficacy endpoints IV-CS reduce infusion reactions, no added benefit with PO-CS HACA rate: placebo=0.7%, RTX500=4.2%, RTX1000=2.7%, but no clinical sequelae	[12]
RTX superior to placebo: ACR20 = 51% vs. 18% Trend to less progression in total Genant-modified Sharp score Significantly less progression in joint space narrowing score Non-serious AEs other than infusion reactions balanced Serious infections: placebo=3.7, RTX=5.2/100 pt-years	[13]
Confirmed similar level of efficacy at week 24 to REFLEX study Further improvement in response rates following retreatment No difference between rituximab doses Better responses if RF or CCP positive at baseline	[15]
Numerically higher ACR response at 48 weeks in arm 3 vs. other two arms Statistically better EULAR response at 48 weeks in arm 3 46% of ACR20 non-responders at 24 weeks responded at 48 weeks (arm 3) Fewer patients had worse response at 48 weeks in arm 3	[14]
RTX + MTX superior to MTX alone in MTX-naïve RA ACR and EULAR responses not affected by RTX dose mTSS progression only significantly better with RTX1000	[16]

EULAR, European League Against Rheumatism; FACIT-F, functional assessment of chronic illness therapy–fatigue; HACA, human antichimeric antibody; HAQ, health assessment questionnaire; Ig, immunoglobulin; IV-CS, intravenous corticosteroid; mTSS, medial tibial stress syndrome; MTX, methotrexate; MTX-IR, methotrexate inadequate response; PO-CS, oral corticosteroid; pt, patient; RF, rheumatoid factor; RTX, rituximab; SF36, Short Form (36) survey; TNF-IR, tumor necrosis factor inadequate response.

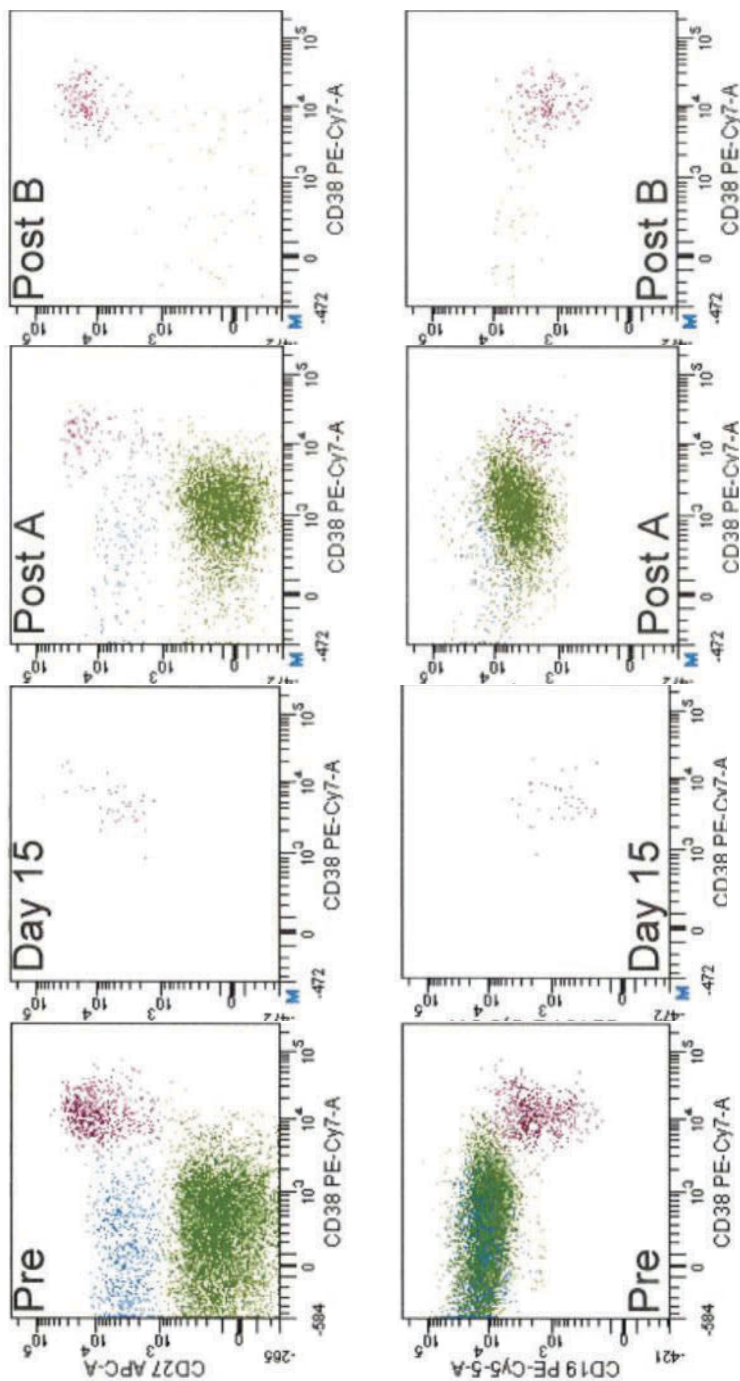


Figure 11.6 Peripheral blood flow cytometry after rituximab. B-cell depletion in peripheral blood after rituximab, as measured by flow cytometry. Extensive sequential gating has been used in a protocol designed to optimize accurate detection of low numbers of B cells, especially plasma cells. B-lineage cells were classified as naïve (CD19+CD27-CD38-, shown in green), memory (CD19+CD27+CD38-, shown in blue) and plasmablast (CD19+/-CD27+/-CD38+/-, shown in purple) with markers to exclude T cells and monocytes. High numbers of plasmablasts at baseline and day 15 were associated with inferior clinical response. Subsets in repopulation varied – two different example repopulation patterns are shown above. Reproduced with permission from Vital et al [18] © Wiley.

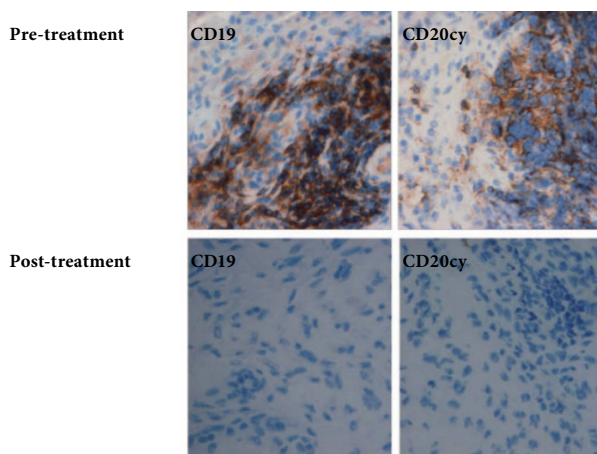


Figure 11.7 Effect of rituximab in the synovium in rheumatoid arthritis. Rituximab is able to clear B cells from the synovium but this does not determine degree of clinical response.

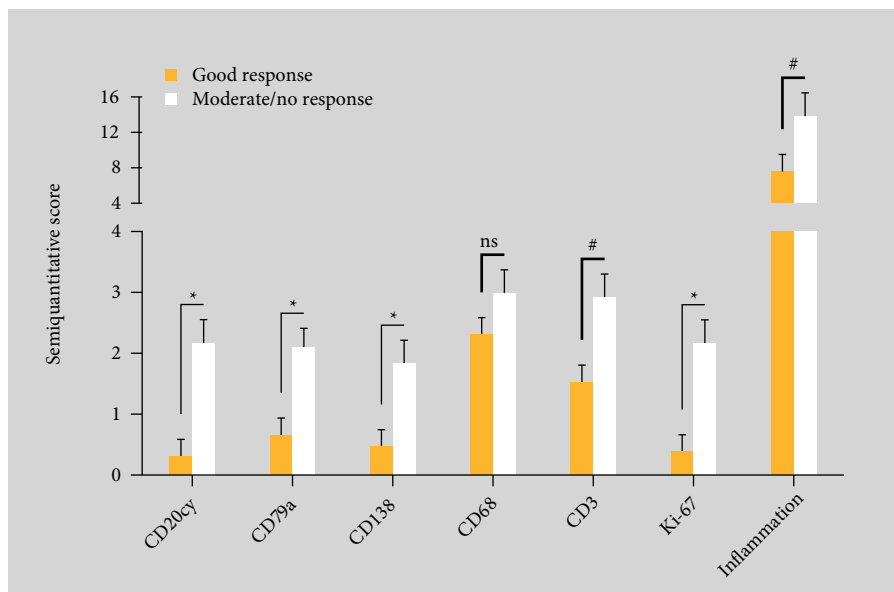


Figure 11.8 Baseline synovial immunohistochemistry and clinical response. Higher scores for a number of immunohistochemical (IHC) markers were associated with failure to achieve a EULAR-designated good response. This was most marked for CD79a+ cells. * $P \leq 0.05$; # $P < 0.10$. ns, not significant. Reproduced with permission from Teng et al [21] ©Wiley.

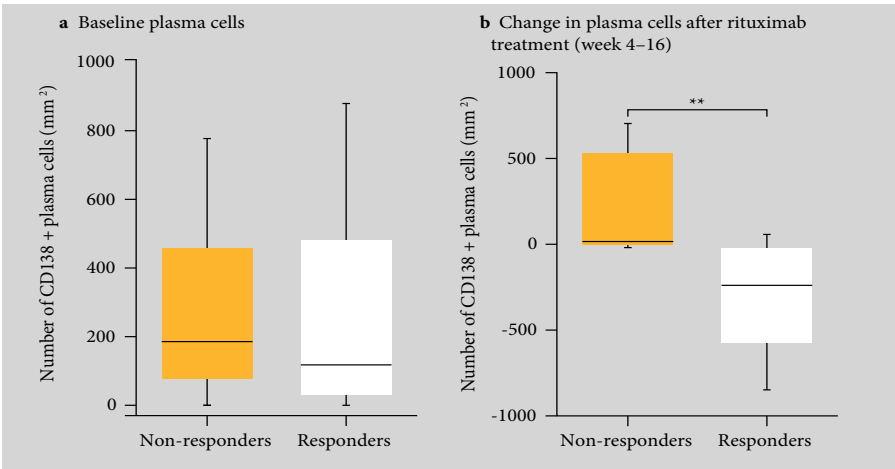


Figure 11.9 Change in synovial plasma cell numbers and clinical response. Early reduction in synovial immunohistochemistry cell counts was not associated with clinical response, but in EULAR responders there was a greater late reduction in synovial CD138+ plasma cells after rituximab treatment. ** $P < 0.01$. Reproduced with permission from Thurlings et al [22] ©BMJ.

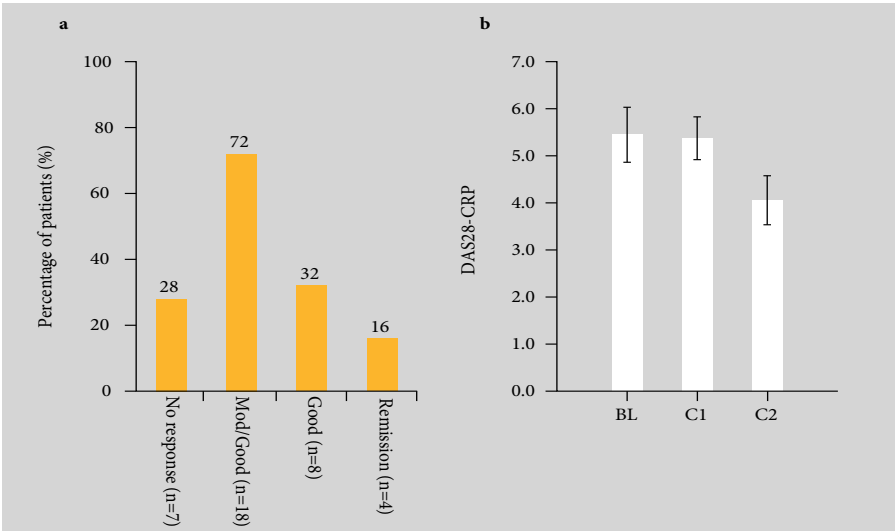


Figure 11.10 Retreating rituximab nonresponse. Clinical responses 6 months after the second cycle of rituximab ($n = 25$) with rheumatoid arthritis that did not respond to the first cycle. (a) EULAR response rates. (b) DAS28 using the C-reactive protein level (DAS28-CRP) measured at baseline, 6 months after cycle 1 (C1), and 6 months after cycle 2 (C2). Given the association between increased baseline numbers of B lineage (BL) subsets in non-responders and the persistence of plasmablasts in blood and plasma cells in the synovium, further cycles of rituximab seems logical in patients who fail to respond to a first. 100% had EULAR nonresponse 6 months after a first cycle and were retreated (2x1000 mg); 72% then had a EULAR response; some achieved a EULAR 'good' response or remission. Retreatment with rituximab may be an effective strategy for patients with initial nonresponse, rather than switching to another biologic. Reproduced with permission from Vital et al [23] ©Wiley.

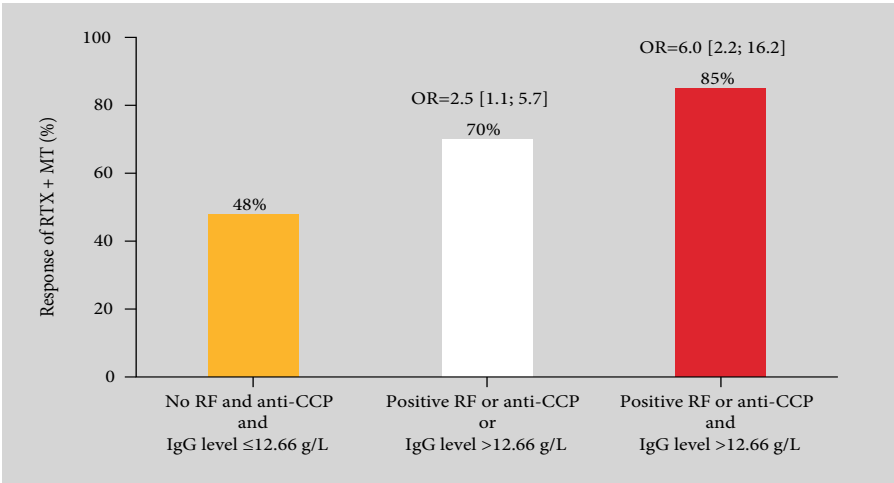


Figure 11.11 B-cell activation markers and response to rituximab. Frequency of EULAR response according to the presence of autoantibodies and an immunoglobulin (Ig) G concentration above the upper limit of normal (ULN) (12.66 g/L). Results are presented as odds ratios (ORs) and 95% confidence intervals for patients having autoantibodies and/or an IgG concentration >ULN compared with patients having no autoantibodies and an IgG concentration ≤ULN. The data shown above indicate that any one of many markers of serological activity (RF, anti-CCP, or high IgG) at baseline indicate disease that is potentially responsive to rituximab (RTX) therapy, and that there is synergism between these indicators. Anti-CCP, anti-cyclic citrullinated proteins; IgG, immunoglobulin G; MTX, methotrexate; RF, rheumatoid factor. Reproduced with permission from Sellam et al [24] ©Wiley.

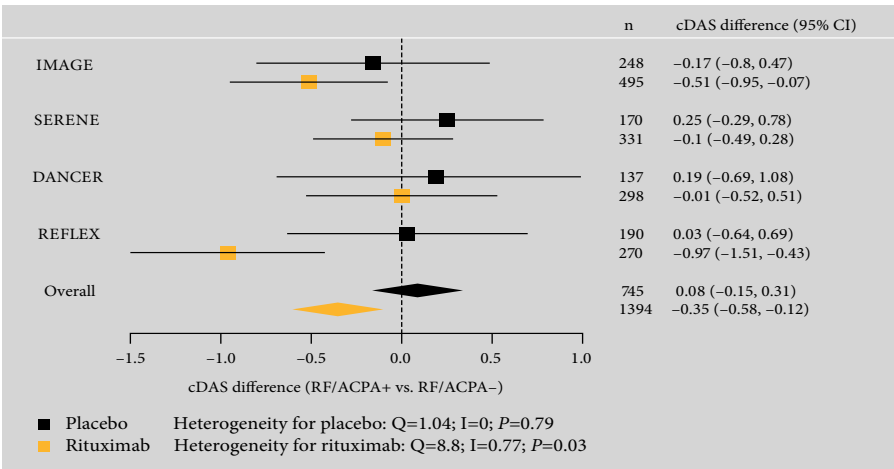


Figure 11.12 Meta-analysis of antibody status and response to rituximab in randomized controlled trials. Meta-analysis of randomized controlled trials comparing difference in change in DAS28 between seropositive and seronegative patients. The overall outcome indicated better responses in seropositive patients, although results were mixed between trials. This probably relates to other differences between populations recruited (for example, the difference was greater in anti-TNF-IR patients). ACAP, anti-citrullinated protein antibody; cDAS change in daily activity score; RF, rheumatoid factor. Reproduced with permission from Isaacs et al [25] ©BMJ.

Safety of repeat cycles

Data from follow up of patients in randomized controlled trials of rituximab in RA are shown in Figure 11.13 [19,26]. Overall infection and serious infection rates appeared to be stable.

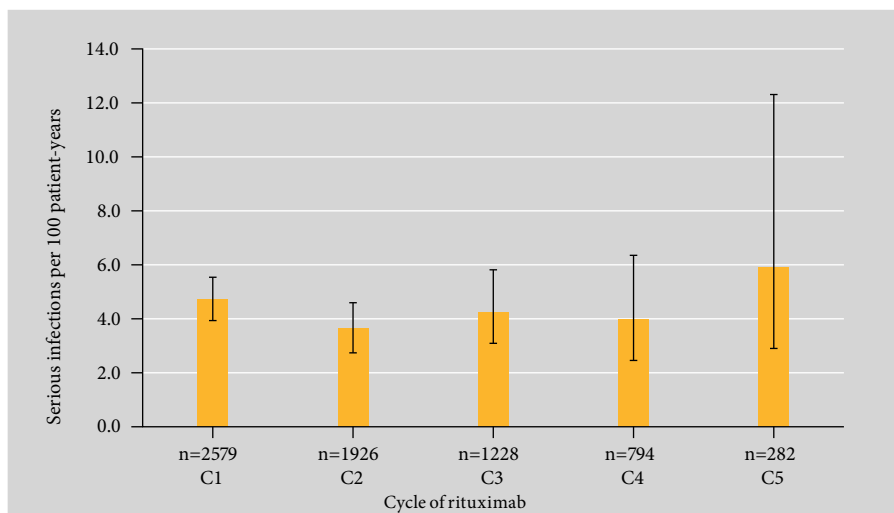


Figure 11.13 Safety of rituximab in rheumatoid arthritis. Data from follow up of patients in randomized controlled trials of rituximab (RTX) in rheumatoid arthritis (RA). Serious infection rate per 100 patient-years and 95% confidence interval are shown. However, there are two important considerations to these data. First, in such long-term follow-up studies, patients may withdraw from treatment due to an adverse event, and so extension data may underestimate adverse event rates. Second, this analysis does not demonstrate infection rates in important subgroups. In an analysis from the French Autoimmunity and Rituximab registry, multivariate analysis showed that chronic lung disease and/or cardiac insufficiency (odd ratio [OR]=3.0, 95% CI, 1.3–7.3; $P<0.01$), RA-related extra-articular involvement (OR=2.9, 95% CI, 1.3–6.7; $P=0.009$), and a low immunoglobulin G level (<6 g/L) before RTX treatment (OR= 4.9, 95% CI, 1.6–15.2; $P<0.005$) were significantly associated with an increased risk of severe infection after RTX infusions. Reproduced with permission from VanVollenhoven et al [26] ©BMJ.

References

1. Hatjiharissi E, Hansen M, Santos DD, et al. Genetic linkage of Fc gamma RIIa and Fc gamma RIIIa and implications for their use in predicting clinical responses to CD20-directed monoclonal antibody therapy. *Clin Lymphoma Myeloma*. 2007;7:286-290.
2. Anolik JH, Campbell D, Felgar RE. The relationship of Fc gamma RIIIa genotype to degree of B cell depletion by rituximab in the treatment of systemic lupus erythematosus. *Arthritis Rheum*. 2003;48:455-459.
3. Di Gaetano N, Cittera E, Nota R, et al. Complement activation determines the therapeutic activity of rituximab in vivo. *J Immunol*. 2003;171:1581-1587.
4. van der Kolk LE, Grillo-Lopez AJ, Baars JW, Hack EE, van Oers MH. Complement activation plays a key role in the side effects of rituximab treatment. *Br J Haematol*. 2001;115:807-811.
5. Cragg MS, Morgan SM, Chan HT, et al. Complement-mediated lysis by anti-CD20 mAb correlates with segregation into lipid rafts. *Blood*. 2003;101:1045-1052.

6. Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MD, eds. *Rheumatology*. 5th edn. Maryland Heights, MO: Mosby; 2011.
7. Firestein GS, Zvaifler NJ. How important are T cells in chronic rheumatoid synovitis? *Arthritis Rheum*. 1990;33:768-773.
8. Edwards JC, Cambridge G. Rheumatoid arthritis: the predictable effect of small immune complexes in which antibody is also antigen. *Br J Rheumatol*. 1998;37:126-130.
9. Mauri C, Ehrenstein MR. Cells of the synovium in rheumatoid arthritis. B cells. *Arthritis Res Ther*. 2007;9:205.
10. Vital E, Kay J, Emery P. Rituximab biosimilars. *Expert Opin Biol Ther*. 2013;13:1049-1062.
11. Edwards JCW, Szczepanski L, Szechinski J, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Eng J Med*. 2004;350:2572-2581.
12. Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheum*. 2006;54:1390-1400.
13. Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy - results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum*. 2006;54:2793-2806.
14. Rubbert-Roth A, Tak PP, et al. Efficacy and safety of various repeat treatment dosing regimens of rituximab in patients with active rheumatoid arthritis: results of a Phase III randomized study (MIRROR). *Rheumatology (Oxford)*. 2010;49:1683-1693.
15. Emery P, Deodhar A, Rigby WF, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders [SERENE]). *Ann Rheum Dis*. 2010;69:1629-1635.
16. Tak PP, Rigby WF, Rubbert-Roth A, et al. Inhibition of joint damage and improved clinical outcomes with rituximab plus methotrexate in early active rheumatoid arthritis: the IMAGE trial. *Ann Rheum Dis*. 2011;70:39-46.
17. Emery P, Mease PJ, Rubbert-Roth A, et al. Retreatment with rituximab based on a treatment-to-target approach provides better disease control than treatment as needed in patients with rheumatoid arthritis: a retrospective pooled analysis. *Rheumatology (Oxford)*. 2011;50:2223-2232.
18. Vital EM, Dass S, Buch MH, et al. B cell biomarkers of rituximab responses in systemic lupus erythematosus. *Arthritis Rheum*. 2011;63:3038-3047.
19. Mei HE, Frolich D, Giesecke C, et al. Steady-state generation of mucosal IgA+ plasmablasts is not abrogated by B-cell depletion therapy with rituximab. *Blood*. 2010; 116:5181-5190.
20. Kerkman P, van der Voort EIH, Trouw LA, Huizinga TWJ, Toes REM, Scherer HU. Circulating plasmablasts as a source of anti-citrullinated protein antibodies in patients with rheumatoid arthritis. *Arthritis Rheum*. 2012;64:S756-S756.
21. Teng YK, Levarht EW, Hashemi M, et al. Immunohistochemical analysis as a means to predict responsiveness to rituximab treatment. *Arthritis Rheum*. 2007;56:3909-3918.
22. Thurlings RM, Vos K, Wijnbrandts CA, Zwinderman AH, Gerlag DM, Tak PP. Synovial tissue response to rituximab: mechanism of action and identification of biomarkers of response. *Ann Rheum Dis*. 2008;67:917-925.
23. Vital EM, Dass S, Rawstron AC, et al. Management of nonresponse to rituximab in rheumatoid arthritis predictors and outcome of re-treatment. *Arthritis Rheum*. 2010;62:1273-1279.
24. Sellam J, Hendel-Chavez H, Rouanet S, et al. B cell activation biomarkers as predictive factors for the response to rituximab in rheumatoid arthritis. *Arthritis Rheum*. 2011;63:933-938.
25. Isaacs JD, Cohen SB, Emery P, et al. Effect of baseline rheumatoid factor and anticitrullinated peptide antibody serotype on rituximab clinical response: a meta-analysis. *Ann Rheum Dis*. 2013; 72:329-336.
26. Van Vollenhoven R, Chatzidionysiou K, Gabay C, et al. Rheumatoid factor predicts response to rituximab in a European registry-based cohort: 6-month results from the collaborative European registries for rituximab in rheumatoid arthritis (CERERRA) [abstract]. *Ann Rheum Dis*. 2009;68(suppl 3):579.

12 Novel therapies in rheumatoid arthritis: small molecules

Josef S. Smolen

Introduction

Whether one looks at joint swelling, joint tenderness and stiffness, joint destruction and deformity, fatigue, or laboratory abnormalities such as elevated acute phase reactant levels or anemia of chronic disease, the signs and symptoms of rheumatoid arthritis (RA) are a consequence of the severe inflammation that governs this disease. Inflammation results from a cascade of events that include many characteristics common to all chronic inflammatory diseases as well as features which are typical (though not necessarily pathognomonic) for a particular disorder, such as RA, that are involved in the process. The inflammatory response of RA comprises an interplay between a variety of cell populations, such as various T-lymphocyte subsets, B cells, neutrophils, macrophages, dendritic cells, fibroblasts, osteoclasts, chondrocytes, as well as soluble molecules, which include autoantibodies and various cytokines. Complex steps of interactions, activations, and amplifications of these cells and molecules are critical for the arthritic process typical of RA to be built-up and sustained (Figures 12.1–12.3) [1–3].

Cells and cytokines as therapeutic targets

While the cause of RA remains enigmatic and the genetic associations are in line with the involvement of both innate and adaptive immune responses [4], the understanding of pathogenetic events associated with RA has significantly increased over the past two decades, leading to targeted therapies that interfere with the inflammatory and destructive response.

These therapies comprise biologic agents, monoclonal antibodies, and receptor constructs, which target specific mediators of inflammation, such as tumor necrosis factor alpha (TNF- α), interleukin (IL)-6 or its receptor, IL-1, B cells (via depletion of CD20 positive cells), and T-cell co-stimulation via inhibition of the CD80/86-CD28 interaction [2]. These therapies are addressed in Chapter 10.

Interestingly, with the exception of a lower responsiveness upon IL-1 inhibition, all of these targeted biologic agents elicit similar clinical, structural, and functional effects in similar patient populations [2,5]. Moreover, the combination of biologic agents directed against different targets (such as inhibition of TNF and IL-1; T-cell co-stimulation and TNF; or TNF and B-cell depletion), does not convey added efficacy, but increased infection rates. This reveals that the extended inhibition of physiological pathways compromises safety, but cannot render better antiarthritic effects, suggesting a bottleneck of a common final pathway in the pathogenesis of RA [5].

On the other hand, with increasing drug experience, patients with RA become less responsive to new therapies, implying that mechanisms beyond those currently targeted may have to be considered [2,5]. At present, however, approximately 40% of patients seen in clinical practice in industrialized countries (and more in less affluent regions) continue to have significantly active disease despite receiving treatment and, consequently, new therapies need to be developed [6]. These new therapies can involve further cytokines (as discussed in Chapter 10) or may focus on intracellular events.

Signal transduction

Most of the therapeutic targets mentioned above constitute cytokines (eg, TNF, IL-6, IL-1) or cell surface molecules such as CD80/86, to which cytotoxic T-lymphocyte antigen 4 (CTLA4)-immunoglobulin (Ig; abatacept), a fusion protein that exerts immunomodulating effects, binds. Most of these molecules serve as ligands for specific receptors. The interaction of a cell surface receptor with its ligand is only the first step toward cell activation. In order to allow for gene activation, a series of events are needed that transduce this initial signal downstream into the nucleus and hence are called signal transduction events. These mechanisms start with the induction of an intracellular enzymatic activity which directly, or via induction of additional enzymes (Figure 12.3), ultimately lead to activation of transcription factors that only then can translocate to the nucleus and activate the transcription of specific genes. The

enzymes involved are mostly phosphotransferases which phosphorylate proteins (kinases), or phosphatases which remove phosphates from proteins. Importantly, one receptor-ligand pair can activate several different (though sometimes interconnected) signal transduction pathways such as TNF activating the mitogen-activated protein kinase (MAPK) and nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) pathway, whilst a particular pathway (eg, MAPK or NFκB) can be induced by a variety of receptors (Figure 12.4).

Regarding the initial steps of intracellular enzyme activation, some receptors have intrinsic enzymatic activity, such as receptor tyrosine kinases. These enzymes are part of the intracellular domain of the receptor and become activated once the ligand attaches to the extracellular binding site, upon which the receptors become phosphorylated. Further signal transduction proteins can then bind and become the next set of activated enzymes in the overall cascade. Other receptors do not have intrinsic enzyme activity, but their intracellular domain changes upon attachment of their ligand to allow binding of intracellular enzymes, which then phosphorylate the receptor, whereupon other proteins can dock and become activated enzymes to further transduce the signal. Tyrosine kinases of this sort are known as nonreceptor tyrosine kinases (eg, Janus kinases [JAKs]).

Janus kinases

The pathogenesis of RA appears to involve activated T cells and proinflammatory cytokines, including IL-6. Interestingly, various lymphokines, such as IL-2, employ receptors that use JAKs for their signal transduction; IL-6 and interferons also activate JAKs. These kinases have been named after the double-faced Roman god Janus because JAKs have two highly similar domains. The JAK family has four members: JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2), which, once the receptor has undergone a conformational change after binding of the respective ligand, dock to each of the receptor chains, now in sufficient proximity to phosphorylate each other and the intracellular part of the receptor. Thus, at least 2 JAKs bind to each cytokine receptor; each of them can activate specific signal transducer and activator of transcription proteins (STATs) (Figure 12.5). There are a total of 7 STATs (STAT 1, 2, 3, 4, 5a, 5b, and 6). After their phosphorylation, STATs form homo- or heterodimers, translocate to the nucleus and bind to specific sites on the DNA to initiate transcription of pertinent genes. Figure 12.6 depicts the cytokines that activate the JAK-STAT pathway, revealing which JAKs are induced by which cytokines and which STATs are subsequently activated. The central

importance of JAKs is indicated by the observation that JAK 3 deficiency is associated with severe combined immunodeficiency [7,8].

Spleen and Bruton's tyrosine kinase

Another kinase that exhibits pivotal importance in the context of the innate and adaptive immune response is spleen tyrosine kinase (Syk). This kinase is involved in signal transduction for such important receptors such as the B-cell receptor, immunoglobulin Fc gamma receptors (FcR γ) via immunoreceptor tyrosine-based activation (ITAM) motifs [9], and even osteoclastogenesis, where ITAM motifs are also involved [10]. Indeed, osteoclast-associated receptor associates with a FcR γ adaptor molecule in the course of osteoclast activation [11]. Thus, Syk is involved in B-cell activation (as needed for autoantibody production), FcR mediated effects (as needed for cell activation via immune complexes), and bony damage (for which osteoclast activation is mandatory).

Another kinase pivotally involved in cells of the immune system is Bruton's tyrosine kinase (Btk) which is linked to the B-cell receptor and also affects macrophage function [12,13]. Targeting this kinase may constitute another potential future path to clinical success in RA.

Inhibiting intracellular signaling pathways

Inhibition of the intracellular signaling pathways has elicited significant interest in various areas, including inflammation. The first tyrosine kinase inhibitor approved for use in RA was imatinib, which blocks Abelson tyrosine kinase, which is related to the development of chronic myelogenous leukemia [14]. Because MAPKs are activated by proinflammatory cytokines such as TNF and IL-1 and involved in chronic inflammatory responses, there was hope that their inhibition could be beneficial in various inflammatory diseases, such as RA. Hitherto, however, there is no evidence of a significant efficacy of such inhibitors, particularly p38-MAPK blockers, although serious infection rates were found increased when compared with controls [15,16].

NF κ B is likewise activated by several proinflammatory cytokines via an enzymatic cascade. While blocking this factor has been effective in experimental models [17], clinical trials have not gone forward, presumably because of the potential toxicity of interfering with this pivotal pathway [18]. Importantly, because these compounds target intracellular molecules, they are usually taken orally, absorbed, and can enter cells to interfere with their targets.

Inhibition of spleen tyrosine kinase

Fostamatinib

The first Syk-inhibitor studied in patients with RA was fostamatinib. In a Phase II study, Weinblatt et al investigated fostamatinib at 100 mg twice-daily or 150 mg daily compared with placebo in patients who had active RA disease despite methotrexate (MTX) therapy [19]. At the higher dose, the American College of Rheumatology (ACR) 20/50/70 responses, which measure improvement in tender and swollen joint counts, amounted to 67%, 43%, and 28%, respectively, and were significantly higher than the respective placebo response rates (Figure 12.7) [19]. Adverse events included diarrhea, infections, neutropenia, and hypertension. In another Phase II trial, Genovese et al investigated fostamatinib in patients who had previously received TNF-inhibitors and found no difference between active treatment and placebo [20]. Although, a post-hoc analysis of patients who had elevated C-reactive protein levels at baseline revealed significant differences between the groups [20]. Importantly in this respect, results of Phase III trials were disappointing, both in terms of insufficient efficacy and adverse events, and this led to discontinuation of the fostamatinib program.

It remains to be seen if other Syk-inhibitors have a different profile. While fostamatinib was not a highly selective Syk-inhibitor, as it appears to interfere with other kinases such as Lck, JAK1, and JAK3 [21], the blockade of this important signaling pathway appears to be efficacious in RA. Studies of more selective Syk inhibitors are currently underway [22].

Inhibition of Janus kinases

Given their activation by so many cytokines, and inhibition proving to be highly efficacious in RA (eg, IL-6) [2], targeting JAKs with specific inhibitors (Jakinibs) is of particular interest.

Tofacitinib

The first JAK-inhibitor approved in the US and many other countries was tofacitinib. Tofacitinib underwent several Phase III trials which involved various populations of patients with RA: established RA with active disease despite MTX or disease-modifying antirheumatic drug (DMARD) therapy, where it was studied as monotherapy or in combination with MTX or DMARDs [23,24]; in patients with established RA with active disease despite prior TNF-inhibitor therapy [25]; and in patients with early RA who were methotrexate-naïve [26].

The clinical results correspond quite well to those observed with biologic agents. In established RA with active disease despite MTX or disease-modifying antirheumatic drugs (DMARDs), ACR 20 response rates at the licensed 5 mg twice-daily dose were approximately 52%; ACR 50 responses 32–37%; and ACR 70 response rates 15–20% at 6 months [23,27]. In patients who had previously used TNF-inhibitors, these response rates were slightly lower at approximately 42%, 27%, and 14%, respectively, at 3 months [25]. As monotherapy in DMARD-IR patients, responses were approximately 60%, 31%, and 15%, respectively, and thus similar to combination therapy [24]. The ACR 50 responses of these respective trials are shown in Figure 12.8.

The Disease Activity Score in 28 joints (DAS28) and the Simplified Disease Activity Index improved to a larger extent [28]. Functional improvement was also similar to that seen in trials of biologic agents, with reductions in Health Assessment Questionnaire Disability Index in the order of 0.4–0.6 [23–27]. With a 10 mg dose of tofacitinib twice daily, progression of joint damage was halted significantly in patients with long-standing disease, while with a 5 mg twice-daily dose, there was a numerical and clinically convincing (albeit statistically not significant) difference in damage progression when compared with placebo (Figure 12.8) [27]. However, in a study in early MTX-naïve patients with RA, a significant inhibition of damage progression was also seen at the 5 mg twice-daily dose [29]. In that trial, ACR 70 response rates amounted to approximately 25% at 5 mg twice daily, a higher level of response than in established RA and what is usually seen for other compounds [29].

The adverse event profile of tofacitinib is generally in line with expectations according to its pharmacological profile of inhibition of several cytokine signal transduction pathways. Infectious complications include herpes zoster (about 4.3 per 100 patient-years), tuberculosis, and cytopenias (lymphopenia $<500/\text{mm}^3$ occurs rarely but may be associated with infectious episodes). Small increases in creatinine, lipid and liver enzymes occur in some patients; these effects appear to be dose dependent [20–24]. Malignancies did not appear to be observed at higher than the population rates. Increases in hemoglobin are not seen to the same extent as with IL-6 or TNF-inhibition and up to 5% of patients experienced dose-dependent decreases in hemoglobin, suggesting that JAK2 (used by erythropoietin for its signaling) may also be inhibited [8]. Overall, more safety information will have to be collected and analyzed in the post-approval period from ongoing studies and registries.

Baricitinib

Another JAK inhibitor currently being studied is baricitinib, which is in Phase III trials. Baricitinib is a JAK1/2 inhibitor and, as can be judged from the currently available data, baricitinib appears to have a similar efficacy and safety profile as tofacitinib [30].

GLPG0634

GLPG0634 is a selective JAK1 inhibitor which has been assessed in a small early Phase II trial which apparently showed efficacy and overall good safety data [31]. However, more information is needed.

Conclusion

The availability of kinase inhibitors for the treatment of RA is a positive advancement for the management of RA. These drugs target molecules and mechanisms involved in the chronic inflammatory and destructive process of RA, namely intracellular signal transduction pathways. They also specifically target particular molecules, although accuracy when distinguishing between enzymes may have to be further improved. These agents are oral drugs which makes their application easy. Importantly, they are essentially as effective as biological agents, although their safety profile has not yet been fully established, as this requires the accrual of information from registries and postmarketing surveillance over several years. To what extent these drugs will change current treatment beyond the use of biological agents will also have to be part of a learning process; like all novel agents, they will be assessed thoroughly by the rheumatologists before and after their introduction into the market.

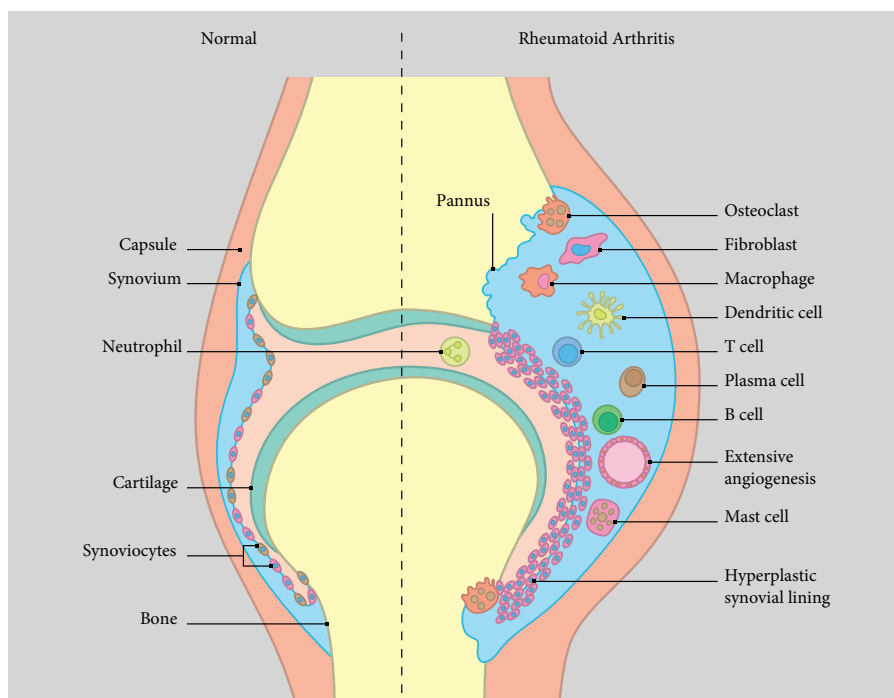


Figure 12.1 Schematic representation of a normal joint and joint with rheumatoid arthritis. The picture shows the thin lining layer and synovial membrane in a normal joint compared with the widened synovial membrane with hyperplasia of the lining layer in rheumatoid arthritis (RA; right half). Many cell populations enter the synovium through activated vasculature (endothelial cells) and contribute to the inflammatory process. B cells, T cells, monocytes/macrophages, and dendritic cells are all part of the process, as are mast cells and synovial fibroblasts. The hyperplastic synovial membrane can invade bone subchondrally and also lead to cartilage destruction. Reproduced with permission from Smolen and Steiner [1] ©Nature.

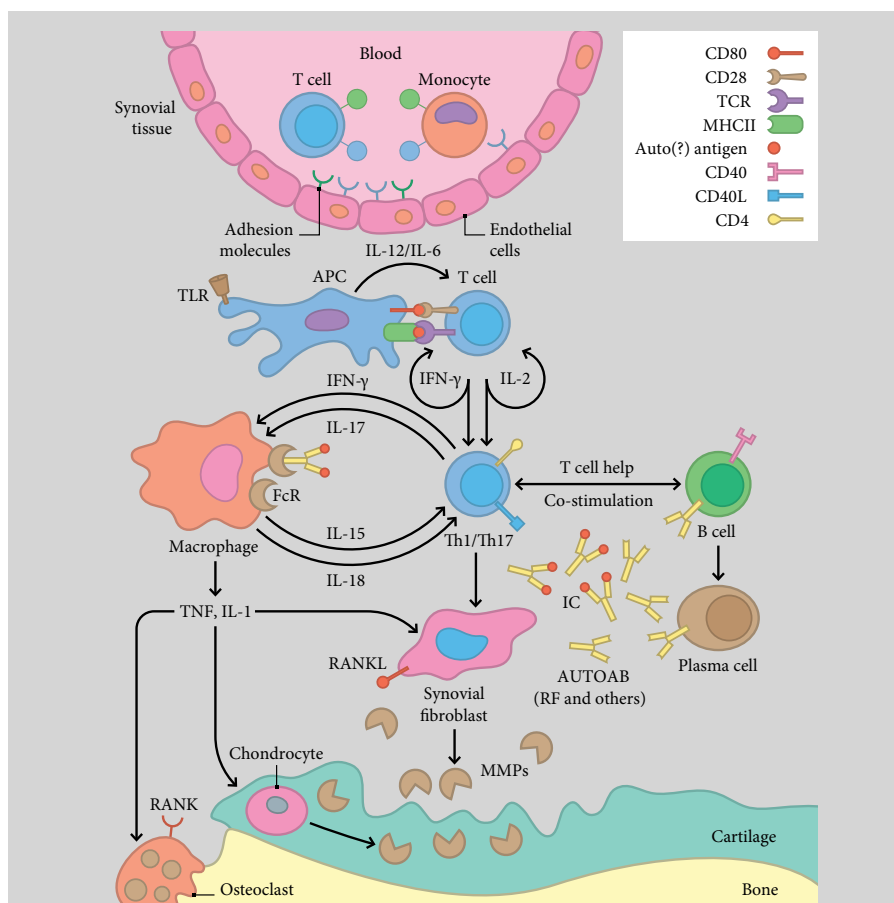


Figure 12.2 Schematic presentation of various cells and molecules and their involvement in rheumatoid arthritis. It is assumed that an unknown antigen is presented by dendritic cells to T-lymphocytes which become activated and express a Th1 or Th17 phenotype. Subsequently, T cells provide help to B cells which mature into plasma cells that secrete autoantibodies such as rheumatoid factor and ACPA; these can form immune complexes and activate complement, and all this leads to activation of macrophages via Fc and complement receptors. Macrophages are also activated by Th1/Th17 cells via various lymphokines, as are synovial fibroblasts. The latter two populations are the main producers of proinflammatory cytokines, which in turn, amplify activation of osteoclasts which destroy bone, and of chondrocytes which damage cartilage. APC, antigen-presenting cells; AUTOAB, autoantibody; CD, cluster of differentiation; FcR, Fc receptor; IC, immune complexes; IL, interleukin; IFN, interferon; MHC, major histocompatibility complex; MMP, matrix metalloproteinases; RANK, receptor activator of nuclear factor kappa-B; RANKL, receptor activator of nuclear factor kappa-B ligand; RF, rheumatoid factor; TCR, T cell receptor; Th1, T helper type 1 cells; TLR, toll-like receptor. Adapted with permission from Smolen and Steiner [1] ©Nature.

a

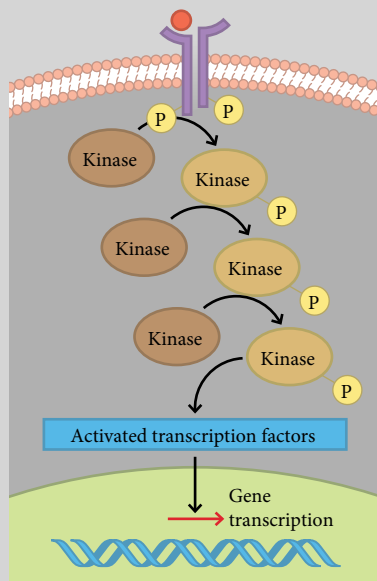


Figure 12.3A Schematic general presentation of signal transduction events from ligation to the receptor ("receptor binding") via activation of a cascade of enzymes and phosphorylation of transcription factors ("signal transduction") and subsequent gene activation. Reproduced with permission from Murphy et al [3] ©Garland Science.

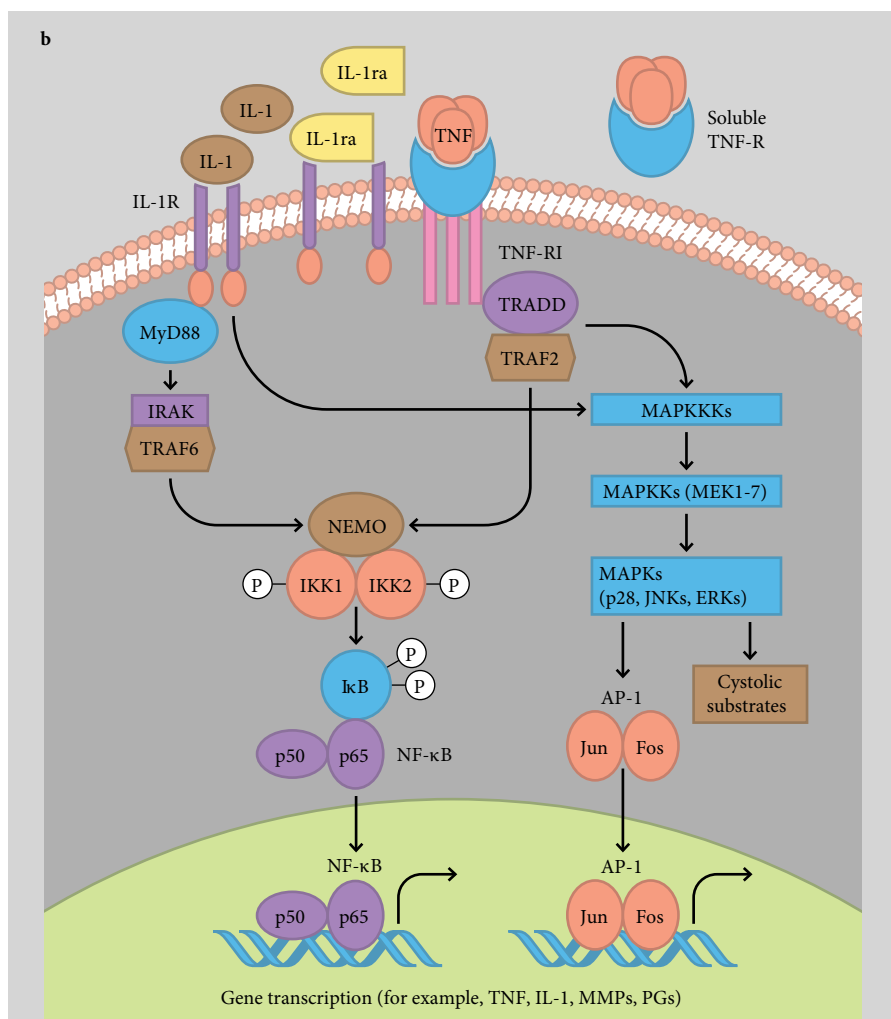


Figure 12.3B Schematic presentation of signal transduction events related to two proinflammatory cytokines, IL-1, and TNF. Generally, one cytokine can activate more than one pathway and different cytokines can activate the same pathway – for example, tumor necrosis factor (TNF) and interleukin (IL)-1. Binding of IL-1 to its receptor will lead to activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) pathway and this will also be the case upon binding of TNF to its receptor; TNF binds as a trimer. In addition, both cytokines will activate the mitogen-activated protein kinase pathway. Both of these pathways will lead to phosphorylation and nuclear translocation of respective transcription factors which will activate specific genes; in the case of IL-1 and TNF, these will primarily be genes involved in the overall inflammatory response. Reproduced with permission from Smolen and Steiner [1] ©Nature.

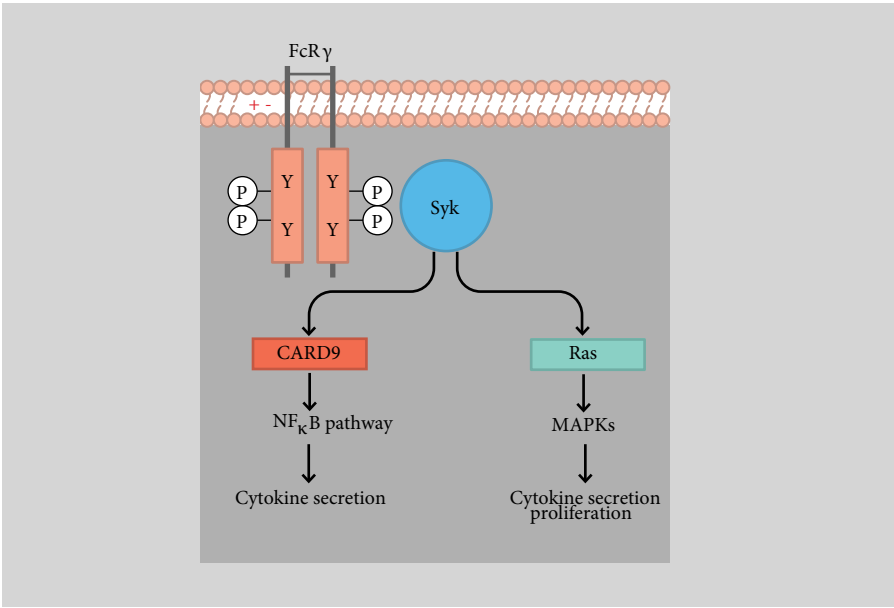


Figure 12.4 Syk kinase induced by Fc receptor gamma also activates NFκB and mitogen-activated protein kinase pathway. CARD9, caspase recruitment domain-containing protein 9; MAPK, mitogen-activated protein kinases; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells. Reproduced with permission from Smolen and Steiner [1] ©Nature.

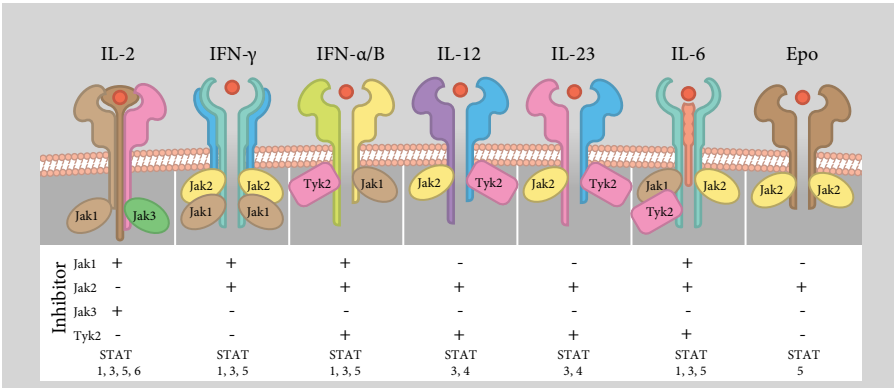


Figure 12.5 Ligands and receptors that use Janus kinases (Jaks). JAKs act as dimers and those activated by specific cytokines/receptors are depicted in the lower half. Note that the same Jak can be used by different receptors, but the pairs usually differ; the pairs can either be heterodimers or homodimers (see erythropoietin [Epo]). IFN, interferon; IL, interleukin; Tyk2, tyrosine kinase 2 deficiency. Adapted with permission from O'Shea and Plenge [8] ©Elsevier.

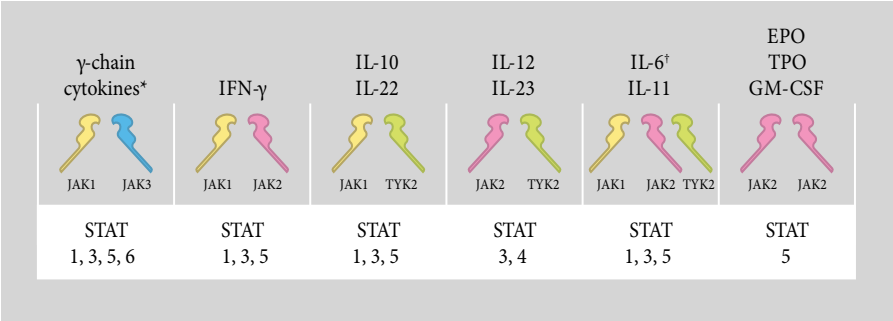


Figure 12.6 Presentation of Janus kinases (Jaks) and respective specific signal transducer and activator of transcription proteins (STATs) used for signal transduction by various cytokines. The STAT molecules that are phosphorylated by the different JAKs are depicted.

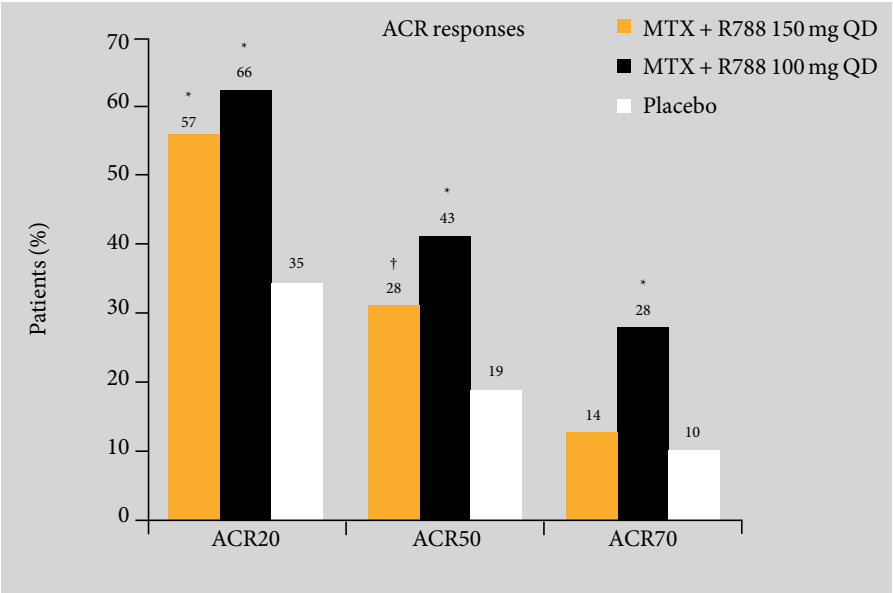


Figure 12.7 Results of spleen tyrosine kinase (Syk) inhibition with fostamatinib. ACR20, 50, and 70 response rates for placebo and two doses of fostamatinib are shown. * $P < 0.01$; † $P < 0.001$. ACR, American College of Rheumatology; ACR 20/50/70, American College of Rheumatology 20%; 50%, and 70% improvement criteria; MTX, methotrexate; QD, once daily. Data from Weinblatt et al [19].

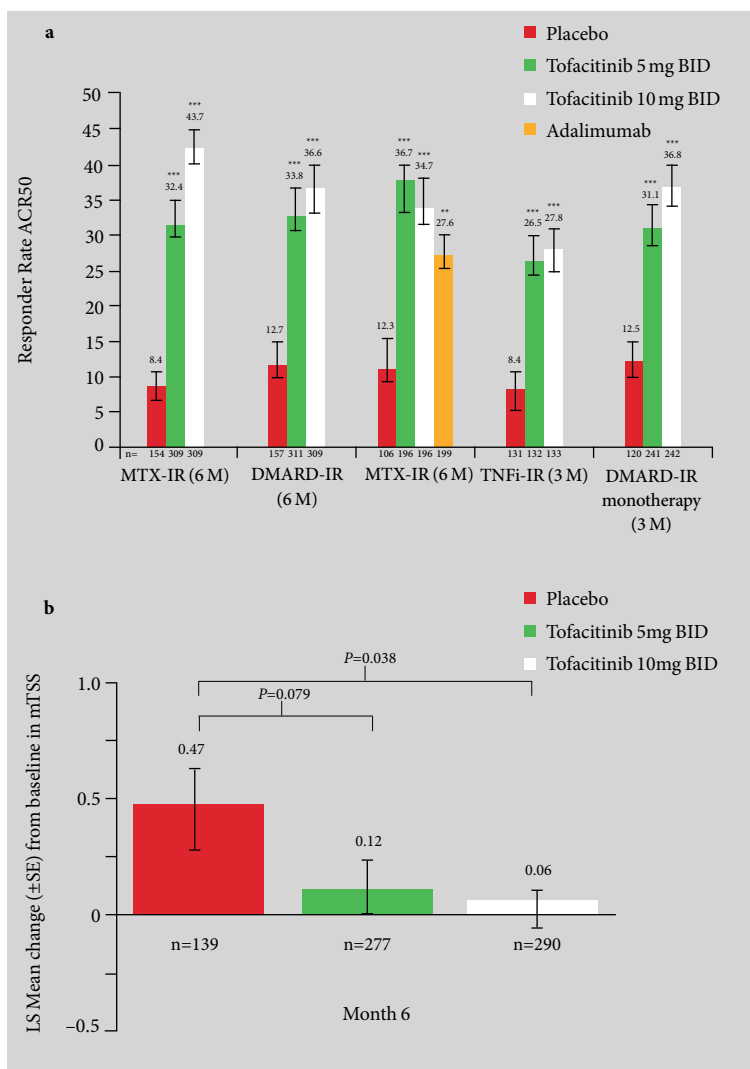


Figure 12.8 Response rates in tofacitinib clinical trials. (a) ACR50 response rates in tofacitinib clinical trials [22,23]. (b) Progression of joint damage. $**P=0.001$; $***P<0.0001$ vs. placebo (unadjusted). ACR50, American College of Rheumatology 50% improvement criteria; BID, twice daily; DMARD, disease-modifying antirheumatic drug; LS, least squares; mTSS, modified total Sharpe score; MTX, methotrexate.

References

1. Smolen JS, Steiner G. Therapeutic strategies for rheumatoid arthritis. *Nat Rev Drug Discov.* 2003;2:473-488.
2. Smolen JS, Aletaha D, Koeller M, Weisman M, Emery P. New therapies for the treatment of rheumatoid arthritis. *Lancet.* 2007;370:1861-1874.
3. Murphy, K. Signaling through immune system receptors. In, *Janeway's Immunobiology.* 7th edn. New York, NY: Garland Science; 2008:219-256.
4. Plenge RM, Bridges SL, Jr. Personalized medicine in rheumatoid arthritis: miles to go before we sleep. *Arthritis Rheum.* 2011;63:590-593.
5. Smolen JS, Aletaha D. Forget personalised medicine and focus on abating disease activity. *Ann Rheum Dis.* 2013;72:3-6.
6. Montag K, Gingold M, Boers A, Littlejohn G. Disease-modifying antirheumatic drug usage, prescribing patterns and disease activity in rheumatoid arthritis patients in community-based practice. *Intern Med J.* 2011;41:450-455.
7. Pesu M, Candotti F, Husa M, Hofmann SR, Notarangelo LD, O'Shea JJ. Jak3, severe combined immunodeficiency, and a new class of immunosuppressive drugs. *Immunol Rev.* 2005;203:127-142.
8. O'Shea JJ, Plenge R. JAK and STAT Signaling molecules in immunoregulation and immune-mediated disease. *Immunity.* 2012;36:542-550.
9. Pamuk ON, Tsokos GC. Spleen tyrosine kinase inhibition in the treatment of autoimmune, allergic and autoinflammatory diseases. *Arthritis Res Ther.* 2010;12:222.
10. Koga T, Inui M, Inoue K, et al T. Costimulatory signals mediated by the ITAM motif cooperate with RANKL for bone homeostasis. *Nature.* 2004;428:758-763.
11. Zawawi MS, Dharmapadni AA, Cantley MD, McHugh KP, Haynes DR, Crotti TN. Regulation of ITAM adaptor molecules and their receptors by inhibition of calcineurin-NFAT signalling during late stage osteoclast differentiation. *Biochem Biophys Res Commun.* 2012;427:404-409.
12. Bajpai UD, Zhang K, Teutsch M, Sen R, Wortis HH. Bruton's tyrosine kinase links the B cell receptor to nuclear factor kappaB activation. *J Exp Med.* 2000; 191:1735-1744.
13. Mukhopadhyay S, Mohanty M, Mangla A, et al. Macrophage effector functions controlled by Bruton's tyrosine kinase are more crucial than the cytokine balance of T cell responses for microfilarial clearance. *J Immunol.* 2002; 168:2914-2921.
14. Kantarjian H, Sawyers C, Hochhaus A, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. *N Engl J Med.* 2002;346:645-652.
15. Cohen SB, Cheng TT, Chindalore V, et al. Evaluation of the efficacy and safety of pamapimod, a p38 MAP kinase inhibitor, in a double-blind, methotrexate-controlled study of patients with active rheumatoid arthritis. *Arthritis Rheum.* 2009;60:335-344.
16. Damjanov N, Kauffman RS, Spencer-Green GT. Efficacy, pharmacodynamics, and safety of VX-702, a novel p38 MAPK inhibitor, in rheumatoid arthritis: results of two randomized, double-blind, placebo-controlled clinical studies. *Arthritis Rheum.* 2009;60:1232-1241.
17. McIntyre KW, Shuster DJ, Gillooly KM, et al. A highly selective inhibitor of I kappa B kinase, BMS-345541, blocks both joint inflammation and destruction in collagen-induced arthritis in mice. *Arthritis Rheum.* 2003;48:2652-2659.
18. Karin M, Lin A. NF-kappaB at the crossroads of life and death. *Nat Immunol.* 2002;3:221-227.
19. Weinblatt ME, Kavanaugh A, Genovese MC, Musser TK, Grossbard EB, Magilav DB. An oral spleen tyrosine kinase (Syk) inhibitor for rheumatoid arthritis. *N Engl J Med.* 2010;363:1303-1312.
20. Genovese MC, Kavanaugh A, Weinblatt ME, et al. An oral syk kinase inhibitor in the treatment of rheumatoid arthritis: a 3 month randomized placebo controlled phase 2 study in patients with active RA who had failed biologic agents. *Arthritis Rheum.* 2011;63:337-345.
21. Braselmann S, Taylor V, Zhao H, et al. R406, an orally available spleen tyrosine kinase inhibitor blocks fc receptor signaling and reduces immune complex-mediated inflammation. *J Pharmacol Exp Ther.* 2006;319:998-1008.

22. Hoellenriegel J, Coffey GP, Sinha U, et al. Selective, novel spleen tyrosine kinase (Syk) inhibitors suppress chronic lymphocytic leukemia B-cell activation and migration. *Leukemia*. 2012;26:1576-1583.
23. van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med*. 2012;367:508-519.
24. Fleischmann R, Kremer J, Cush J, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med*. 2012;367:495-507.
25. Burmester GR, Blanco R, Charles-Schoeman C, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. *Lancet*. 2013;381:451-460.
26. Lee EB, Fleischmann RM, Hall S, et al. Radiographic, clinical and functional comparison of tofacitinib monotherapy versus methotrexate in methotrexate-naïve patients with rheumatoid arthritis. *Arthritis Rheum*. 2012;64(suppl):S1049
27. van der Heijde D, Tanaka Y, Fleischmann R, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis on methotrexate: 12-month data from a 24-month Phase 3 randomized radiographic study. *Arthritis Rheum*. 2013;65:559-570.
28. Smolen JS, Aletaha D. Interleukin-6 receptor inhibition with tocilizumab and attainment of disease remission in rheumatoid arthritis: The role of acute-phase reactants. *Arthritis Rheum*. 2011;63:43-52.
29. Lee EB, Fleischmann RM, Hall S, et al. Radiographic, clinical and functional comparison of tofacitinib monotherapy versus methotrexate in methotrexate-naïve patients with rheumatoid arthritis. *Arthritis Rheum*. 2012;64:S1049.
30. Genovese MC, Keystone E, Taylor P, et al. 24-week results of a blinded phase 2b dose-ranging study of baricitinib, an oral janus kinase 1/janus kinase 2 inhibitor, in combination with traditional disease modifying antirheumatic drugs in patients with rheumatoid arthritis. *Arthritis Rheum*. 2012;64:S1049-S1050.
31. Vanhoute F, Mazur M, van der Aa A, Wigerinck P, van't Klooster G. Selective JAK1 inhibition in the treatment of rheumatoid arthritis: proof of concept with GLPG0634. *Arthritis Rheum*. 2012;60:S1051.